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14. ABSTRACT DARPA's DSO has expressed interest in technologies to engineer field medical therapies at the point of care, such as production of multiple drugs from a single precursor and to drastically reduce the logistics burden of medical treatment in the field. Pharmacy on Demand (POD) is proposed as a fieldable system for synthesizing Active Pharmaceutical Ingredients (APIs) with the intent of significantly reducing the weight and volume of drug products deployed to theatre. To assess the initial feasibility of POD, synthetic routes to three APIs, ibuprofen, atropine and ciprofloxacin, have been devised. The efficiency of synthesis of two, ibuprofen and atropine, has been determined experimentally. The weight of materials used in					
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## Report Title

Pharmacy on Demand Feasibility Assessment Final Report

### ABSTRACT

DARPA's DSO has expressed interest in technologies to engineer field medical therapies at the point of care, such as production of multiple drugs from a single precursor and to drastically reduce the logistics burden of medical treatment in the field. Pharmacy on Demand (POD) is proposed as a fieldable system for synthesizing Active Pharmaceutical Ingredients (APIs) with the intent of significantly reducing the weight and volume of drug products deployed to theatre. To assess the initial feasibility of POD, synthetic routes to three APIs, ibuprofen, atropine and ciprofloxacin, have been devised. The efficiency of synthesis of two, ibuprofen and atropine, has been determined experimentally. The weight of materials used in these syntheses has been compared to the weights of the same APIs in normal dosage form with packaging in order to quantify potential reduction of logistics burden. At the current state of development these new synthetic routes are not efficient enough to offset the weight of excipients and packaging now used to deploy these drugs. Therefore the initial acceptable metrics have not been achieved. Further analysis of wastes resulting from the new synthetic routes is recommended. Beneficial reuse of waste may improve the effective value of the new synthetic routes.

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**List of papers submitted or published that acknowledge ARO support during this reporting period. List the papers, including journal references, in the following categories:**

**(a) Papers published in peer-reviewed journals (N/A for none)**

Number of Papers published in peer-reviewed journals:

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**(c) Presentations**

Number of Presentations:

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**Non Peer-Reviewed Conference Proceeding publications (other than abstracts):**

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

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**Peer-Reviewed Conference Proceeding publications (other than abstracts):**

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

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**(d) Manuscripts**

Number of Manuscripts:

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Number of Inventions:

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**Graduate Students**

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The number of undergraduates funded by this agreement who graduated during this period: ..... 0.00

The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:..... 0.00

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Total Number:

**Names of personnel receiving PHDs**

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Total Number:

**Names of other research staff**

<u>NAME</u>	<u>PERCENT_SUPPORTED</u>
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Total Number:	

**Sub Contractors (DD882)**

**Inventions (DD882)**



# **Pharmacy on Demand Feasibility Assessment Final Report**

**US Army RDECOM Contract W911NF-07-C-0033**

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19 July 2008

## 1. Introduction

This final report covers work performed under US Army RDECOM Contract W911NF-07-C-0033. Pharmacy on Demand (POD) is a seedling effort intended to support DARPA DSO's efforts to significantly reduce the logistics burden of medical treatment in the field. The goal of the seedling effort is to assess the efficiency with which several Active Pharmaceutical Ingredients (APIs) may be produced by common synthetic routes, in theatre. The primary measure of efficiency is the Reaction Mass Efficiency (RME) which is defined as the percentage of the mass of reactants in the final API, accounting for solvent and stoichiometry. A comparison can then be made to the mass efficiency of deploying the same APIs to theatre in current dosage forms and packaging. For POD to be a feasible concept the RME for synthesizing APIs in theatre must be greater than the equivalent mass efficiency of current deployment methods. Atropine, ciprofloxacin and ibuprofen are the APIs chosen for initial evaluation. These API's represent anti-cholinergic, antibiotic and analgesic classes of drugs that are often deployed to theatre.

## 2. Summary of Accomplishments

### *2.1 Project Organization and Schedule*

The seedling effort was divided into four tasks. The first is to design synthetic routes to three APIs, in different classes, maximizing commonality of the routes, starting compounds and reagents. The second is to verify the new synthetic routes to two APIs in batch mode with standard laboratory glassware. The third is to verify these two synthetic routes in a prototype continuous flow reactor. The fourth is to estimate the potential reduction in weight and volume of pharmaceutical materials deployed to theatre based on the results of the first three tasks. The first three tasks were completed. The fourth task was eliminated by a contract modification based on results achieved in the first three tasks..

### *2.2 Task 1*

Task 1 was completed. Synthetic routes to ibuprofen, atropine and ciprofloxacin were designed and atom efficiencies calculated. These three APIs represent a pain reliever, an anticholinergic and an antibiotic, respectively. We speculated that the logistics burden would be best reduced by minimizing the number of starting compounds and reagents. Several routes with high degrees of commonality were considered for each API. Routes using acetic anhydride as a common acyl source with a first step of Friedel-Crafts acylation, catalyzed with aluminum trichloride, were determined to be most promising. Routes of three, seven and six steps were devised from this common starting point for ibuprofen, atropine and ciprofloxacin, respectively. Overall atom efficiencies for the three syntheses were calculated to be 41% for ibuprofen, 43% for atropine and 33% for ciprofloxacin. These atom efficiencies are poor and indicated that commonality of starting compounds and reagents may not be the best approach to reducing the amount of pharmaceutical materials deployed to theatre.

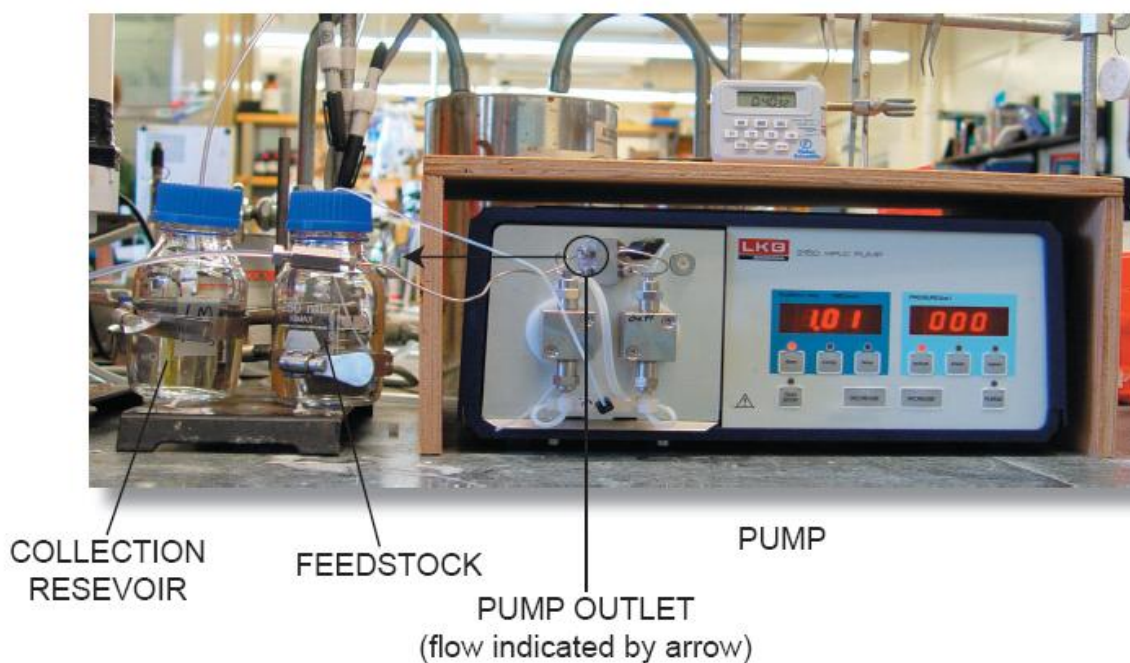
### *2.3 Task 2*

Task 2 was also completed. The approach of maximizing commonality of starting compounds and reagents has proven difficult. Several iterations on the synthetic routes postulated in Task 1 have resulted in no reactions. Therefore alternative routes were evaluated in standard laboratory glassware in favor of optimizing atom efficiency for the reactions in place of maximizing commonality of starting compounds. Approximately 20 variations on catalysts and process conditions for synthesis of ibuprofen were evaluated in the laboratory. The best combination to date gives 85 % atom efficiency for ibuprofen. Subsequently additional combinations of catalyst and process conditions were tested with the goal of reducing the toxicity of waste products however no improvement has been realized at this time. The batch synthesis of atropine is not yet complete but has undergone much iteration. A four step synthesis has been designed and the first two steps have a net atom efficiency of 65% for synthesis of an intermediate product. To date the final two steps have not produced atropine however several experiments are planned to be completed over the next few weeks.

#### **2.4 Task 3**

Task 3 was also completed. The original intent of this task was to convert the batch syntheses demonstrated in Task 2 to a continuous flow method more representative of a likely future implementation of POD. The original plan was to build a new flow reactor. In an attempt to accelerate the schedule an existing flow reactor at Cornell was used. The flow reactor at Cornell is illustrated in the following figures.

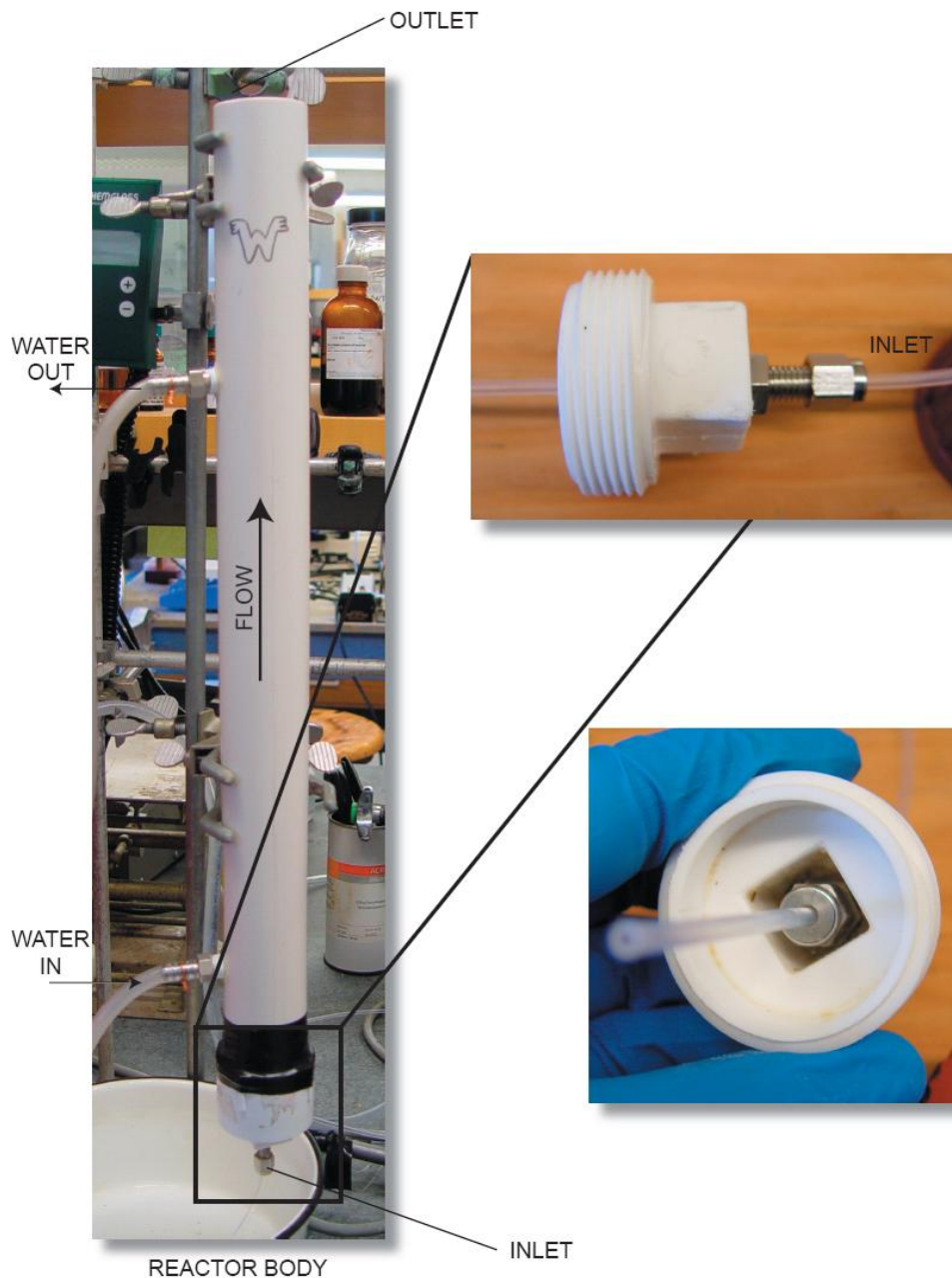
**Figure 1**  
**Image of HPLC Pump and Feedstock and Collection Reservoirs**



This example of the prototype flow reactor, shown in Figure 1, is designed for use in reactions that require only one feedstock (i.e. all reagents can be pre-mixed before

entering the reactor body). The feedstock is supplied to the reactor body using a standard HPLC pump that allows for modulation of the flow rate (in this case,  $0.01 \text{ mL} \cdot \text{min}^{-1}$  –  $9.99 \text{ mL} \cdot \text{min}^{-1}$ ). After the reagents proceed through the temperature controlled reactor body, the output is collected in the collection reservoir.

**Figure 2**  
**Image of the Reactor Body and Bulkhead Fitting for the Reactor Channels**



The shell of the prototype reactor body was constructed from PVC pipe and fitted with an inlet and outlet for the supply and return of temperature controlled liquid (water in this case). The reagents were pumped into the fluorinated reactor channels via the HPLC

pump. The fluorinated reactor channels were sealed using a stainless steel bulkhead fitting, as shown in the right side of Figure 2.

**Figure 3**  
**Temperature Controller and Circulating Pump**



The temperature of the reactor body shell was controlled using a Thermomix heater and a circulating pump (blue pump head shown in Figure 3). These components of the prototype flow reactor will be replaced with a standard heated/cooled circulating bath that will have an available temperature range of -20 °C – 200 °C and will have a circulating pump built in.



**Figure 4**  
**Overall Prototype Flow Reactor**



This image shows the overall prototype flow reactor design. The major components are the HPLC pump, the reactor body shell, the reactor channels, the temperature controller and the circulating pump.

Ibuprofen and atropine were both synthesized successfully in this prototype flow reactor. Atom Efficiency, E-Factor and Reaction Mass Efficiency (RME) were determined for both batch and flow processes. The results are summarized in Table 1.

**Table 1**  
**Summary of Results for Tasks 2 and 3**

	<b>Atom Economy</b>	<b>E-Factor</b>	<b>RME</b>
Ibuprofen (batch)	0.19	25.4	0.04
Ibuprofen (flow)	0.19	8.3	0.11
Atropine (batch)	0.20	Not Calculated	Not Calculated
Atropine (flow)	0.20	15.9 (1 <sup>st</sup> 3 steps)	0.06 (1 <sup>st</sup> 3 steps)

### **2.5 Task 4**

Task 4 was partially completed at the time the project was ended by contract modification.. In this task the RME values shown in Table 1 above were compared to equivalent efficiencies with which the same APIs are deployed to theatre in standard dosage forms and packaging. A component of this analysis is to compare the purity of the APIs synthesized in Task 3 to that of commercially pure products. This analysis is necessary to determine the need for post-synthesis operations that the future POD must perform. Standards for ibuprofen and atropine were procured to form the basis for an analysis of purity of the newly synthesized compounds. Data for the purity analysis are derived from HPLC spectroscopy. The preliminary analysis of potential weight savings is not encouraging. The effective RME for ibuprofen in standard dosage form and packaging is approximately 0.38, based on an analysis of Motrin IB™ delivery in 100 tablet bottles and 200 mg dosage strength. Therefore the efficiency of flow synthesis of ibuprofen is less than one third of the level needed to begin to create a weight budget for a future POD system.

### **3. Major Accomplishments and Problems**

The major accomplishments have been completion of work envisioned under Tasks 1 through 3 with the exception of building a second flow reactor. By using the existing flow reactor at Cornell we were able to produce all experimental data planned for this project. A significant problem is the RME values achieved for flow synthesis of atropine and ibuprofen. The RME values summarized above in Table 1 compare favorably to those achieved in traditional pharmaceutical manufacturing in batch processes. However RME values will have to improve by factors of more than 4.0 to indicate that POD is a feasible concept. Alternative analyses, including beneficial reuse of wastes should be considered.

### **4. Actual Expenditures**

Total expenditures were \$203,592 or 69% of the authorized total of \$274,484 at the time that the project was ended by contract modification. Spending matched the planned levels with the exception of not building the second flow reactor as discussed above. All data that would have been generated using the second reactor have been generated using an existing system at Cornell University.

## Appendices

### Appendix 1 – Systanix First Progress Report

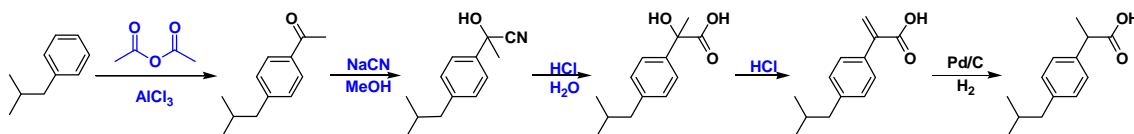
#### I. API SYNTHETIC DESIGN

##### A. Common Chemistry

The three syntheses described below were designed with the intent of using as many similar reagents as possible. Decreasing the number of necessary reagents inherently reduces the amount of material that needs to be transported into the field. Another important advantage of maximizing the number of common reactions is that the number and type of materials needed for purification are also reduced. In Schemes 1-3, common reagents are denoted in blue. It can be seen that all three pathways begin with the same Friedel-Crafts transformation and Schemes 1 and 2 rely on common conditions for the first four steps. These pathways provide flexible access to three important classes of active pharmaceutical ingredients (pain reliever, anticholinergic, and antibiotic) by maximizing commonalities in the synthetic pathways.

##### B. Ibuprofen

The five-step pathway to synthesize ibuprofen (Scheme 1) begins with an aluminum trichloride catalyzed Friedel-Crafts acylation, using acetic anhydride as the acyl source. The resulting ketone is treated with sodium cyanide to form



**Scheme 1.** Proposed synthetic pathway to produce ibuprofen.

the cyanohydrin product, which is subsequently hydrolyzed and dehydrated to provide the acrylic acid containing species. The final step in this pathway utilizes a palladium-catalyzed hydrogenation of the double bond, yielding ibuprofen. An analysis of this ibuprofen synthetic pathway indicates that the overall atom economy is 41% (Table 1).

**Table 1.** Atom economy analysis of the ibuprofen synthetic pathway.

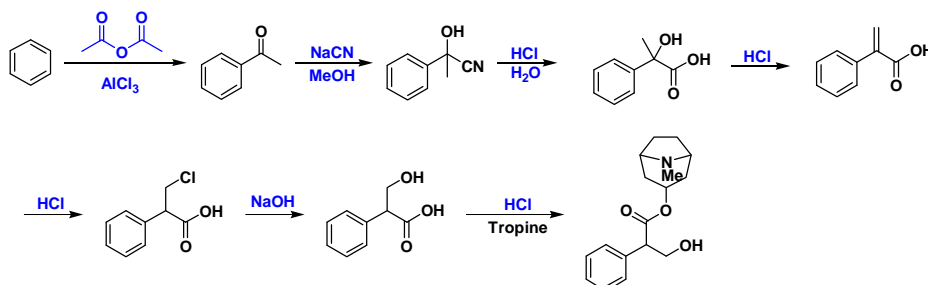
Step	1	2	3	4	5	Overall
A.E.	45%	79%	93%	81%	100%	41%

##### C. Atropine

The seven-step pathway to produce atropine (Scheme 2) begins with a Friedel-Crafts acylation catalyzed by aluminum trichloride, again using acetic anhydride as the acyl source. The resulting ketone is treated with sodium



cyanide to form the cyanohydrin product. A sequential hydrolysis-dehydration results in an acrylic acid moiety. Subsequent chlorination produces an alkyl chloride moiety, which is hydrolyzed to provide the resulting alcohol-containing species (tropic acid). The final step involves a Fischer esterification between tropic acid and tropine to provide atropine. An analysis of this atropine synthetic



pathway indicates that the overall atom economy is 43% (Table 2).

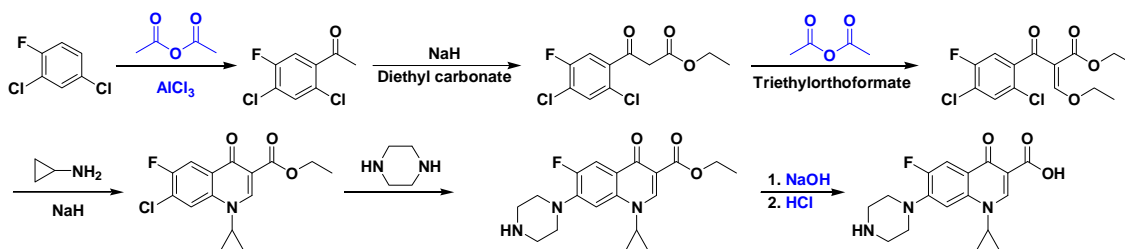
**Scheme 2.** Proposed synthetic pathway to produce atropine.

**Table 2.** Atom economy analysis of the atropine synthetic pathway.

Step	1	2	3	4	5	6	7	Overall
A.E.	36%	73%	98%	89%	100%	74%	94%	43%

#### D. Ciprofloxacin

The six-step synthetic pathway to produce ciprofloxacin (Scheme 3) begins with a Friedel-Crafts acylation catalyzed by aluminum trichloride, using acetic anhydride as the acyl source. The resulting ketone is deprotonated with sodium hydride and treated with diethyl carbonate, forming the Claisen product.



**Scheme 3.** Proposed synthetic pathway to produce ciprofloxacin.

Subsequent treatment with triethylorthoformate in the presence of acetic anhydride results in the formation of the alkylidene product. A tandem displacement-ring closing sequence follows, providing the quinolone structure. The synthesis is completed with a nucleophilic aromatic substitution with piperazine, followed by saponification and acidification. An analysis of this atropine synthetic pathway indicates that the overall atom economy is 33% (Table 3).

**Table 3.** Atom economy analysis of the ciprofloxacin synthetic pathway.

Step	1	2	3	4	5	6	Overall
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<b>A.E.</b>	49%	80%	63%	74%	91%	88%	33%
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## II. FEASIBILITY ASSESSMENT: BATCH CHEMISTRY

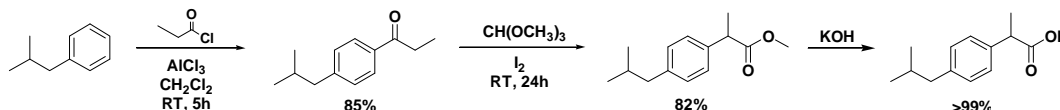
### A. Definition

Two APIs from Section I, ibuprofen and atropine, were selected for an initial demonstration of synthesis using classical batch chemistry. The following subsections will describe the current status of this portion of the project. The most successful routes to date, as well as unsuccessful routes encountered during this investigation are presented below. For each API, a justification is provided for deviations from the original syntheses described in Section I.

### B. Ibuprofen

Ibuprofen has been *successfully synthesized in batch mode* using the three-step route shown in Scheme 4. In comparison to the originally proposed synthesis this process requires fewer steps and obviates the need for sodium cyanide and palladium, which are toxic and environmentally harmful reagents. This synthesis affords ibuprofen in a very efficient 70% overall yield. More importantly for the scope of this project, several reagents used in this route can be applied to the synthesis of atropine (described later).

#### 1. Most Successful Route

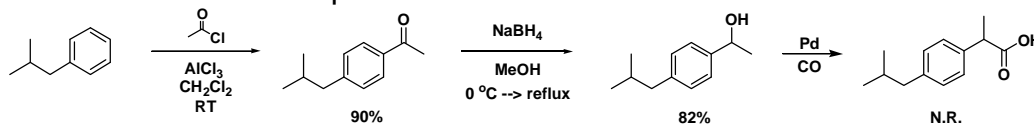


**Scheme 4.** Completed batch route to ibuprofen.

#### 2. Attempted Routes

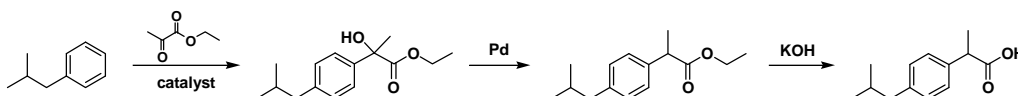
This section describes unsuccessful attempts at synthesizing ibuprofen. Schemes 5-9 illustrate the conceptual routes that were investigated. The information listed in Tables 4-7 describes the failed attempts at completing the first step in each of the respective synthetic pathways. In each scenario that a route was met with failure, a new route was designed with the overall goals of the POD project in mind: synthetic efficiency and the use of common reagents with respect to the synthesis of atropine.

##### a. Initial batch attempt



**Scheme 5.** Initially attempted batch route to ibuprofen.

##### b. Ethyl pyruvate route

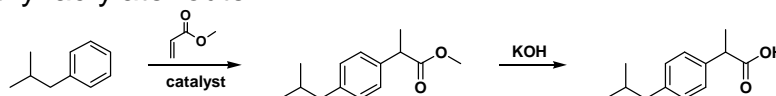


**Scheme 6.** Overall synthetic design of the ethyl pyruvate route.

**Table 4.** Results of the first step of the ethyl pyruvate route to ibuprofen.

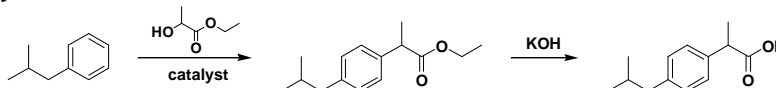
Catalyst	Pertinent Reaction Conditions	Result
TfOH (20 mol %)	CH <sub>2</sub> Cl <sub>2</sub> , Reflux	N.R.
TfOH (20 mol %)	CH <sub>2</sub> Cl <sub>2</sub> , Slow pyruvate addition, Reflux	N.R.
TfOH (20 mol %)	Neat, 105 °C	N.R.
TfOH (20 mol %)	CH <sub>2</sub> Cl <sub>2</sub> , Sealed vessel, 90 °C,	N.R.
Solid-supported TfOH	CH <sub>2</sub> Cl <sub>2</sub> , Reflux	N.R.
SnCl <sub>4</sub> (1.5 eq)	CH <sub>2</sub> Cl <sub>2</sub> , 0 °C to R.T.	N.R.
AlCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T., N <sub>2</sub>	N.R.
TiCl <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T., N <sub>2</sub> Atmosphere	N.R.
BF <sub>3</sub> OEt <sub>2</sub>	Neat, R.T.	N.R.
TiCl <sub>4</sub> + Al <sub>2</sub> O <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T.	N.R.
BF <sub>3</sub> OEt <sub>2</sub> + Al <sub>2</sub> O <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T.	N.R.
AlCl <sub>3</sub> + Al <sub>2</sub> O <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T.	N.R.

## c. Methyl acrylate route

**Scheme 7.** Overall synthetic design of the methyl acrylate route.**Table 5.** Results of the first step of the methyl acrylate route to ibuprofen.

Catalyst	Pertinent Reaction Conditions	Result
AlCl <sub>3</sub> (1.5 eq)	CH <sub>2</sub> Cl <sub>2</sub> , R.T., N <sub>2</sub> Atmosphere	N.R.
AlCl <sub>3</sub> (1.5 eq)	CH <sub>2</sub> Cl <sub>2</sub> , HCl (g), R.T., N <sub>2</sub> Atmosphere	N.R.
AlCl <sub>3</sub> (1.5 eq)	CH <sub>2</sub> Cl <sub>2</sub> , HCl (aq), R.T., N <sub>2</sub> Atmosphere	N.R.
SnCl <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T., N <sub>2</sub> Atmosphere	N.R.
TiCl <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T., N <sub>2</sub> Atmosphere	N.R.
BF <sub>3</sub> OEt <sub>2</sub>	Neat	N.R.
AlCl <sub>3</sub> + Al <sub>2</sub> O <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T.	N.R.

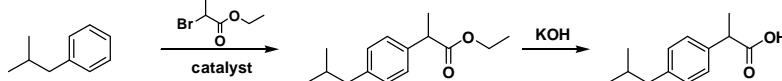
## d. Ethyl lactate route

**Scheme 8.** Overall synthetic design of the ethyl lactate route.

**Table 6.** Results of the first step of the ethyl lactate route to ibuprofen.

Catalyst	Pertinent Reaction Conditions	Result
H <sub>2</sub> SO <sub>4</sub> (aq. 80%)	75 °C	N.R.
AlCl <sub>3</sub> + Al <sub>2</sub> O <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T.	N.R.
TfOH	80 °C, sealed vessel	N.R.

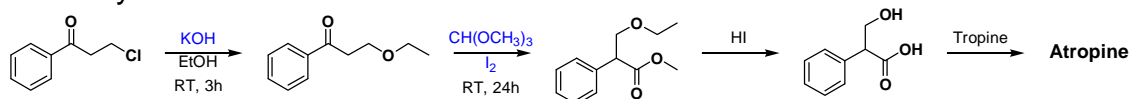
## e. Ethyl 2-bromopropionate route

**Scheme 9.** Overall synthetic design of the ethyl 2-bromopropionate route.**Table 7.** Results of the first step of the ethyl 2-bromopropionate route to ibuprofen.

Catalyst	Pertinent Reaction Conditions	Result
AlCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T.	N.R.
AlCl <sub>3</sub> + Al <sub>2</sub> O <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> , R.T.	N.R.
TfOH	80 °C, Sealed vessel	N.R.

**C. Atropine**

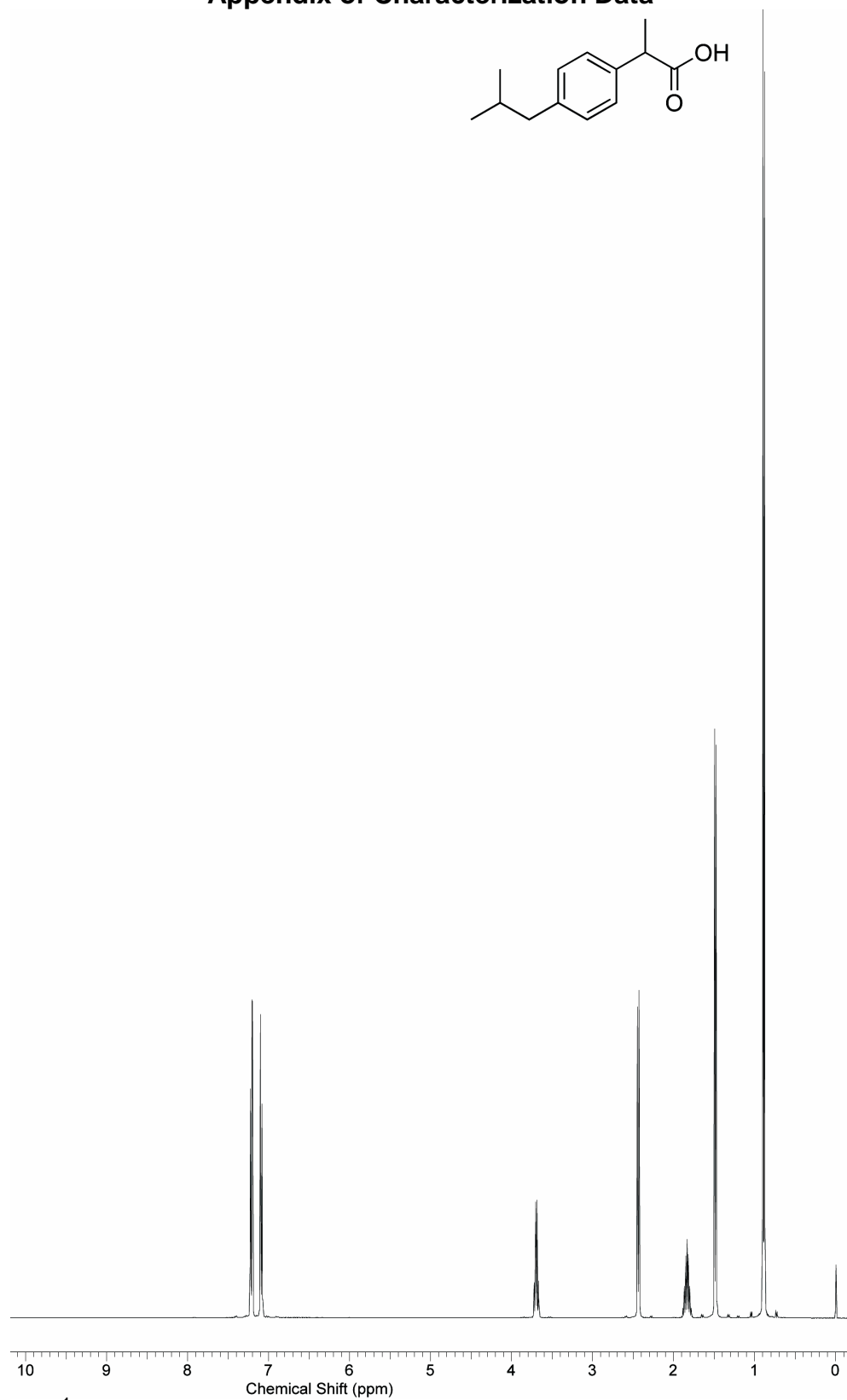
The second API chosen for the batch chemistry feasibility study is atropine. The pathway shown in Scheme 10 is a result of synthetic redesign based on the successful ibuprofen synthesis (described above). The reagents highlighted in blue are common with the ibuprofen pathway. The synthesis begins with a base-catalyzed etherification, followed by an oxidative 1,2-aryl migration. A tandem deethylation-ester hydrolysis generates tropic acid, which is then coupled with tropine to form atropine. Exploratory work on this route is underway.

**Scheme 10.** Redesigned synthesis of atropine.

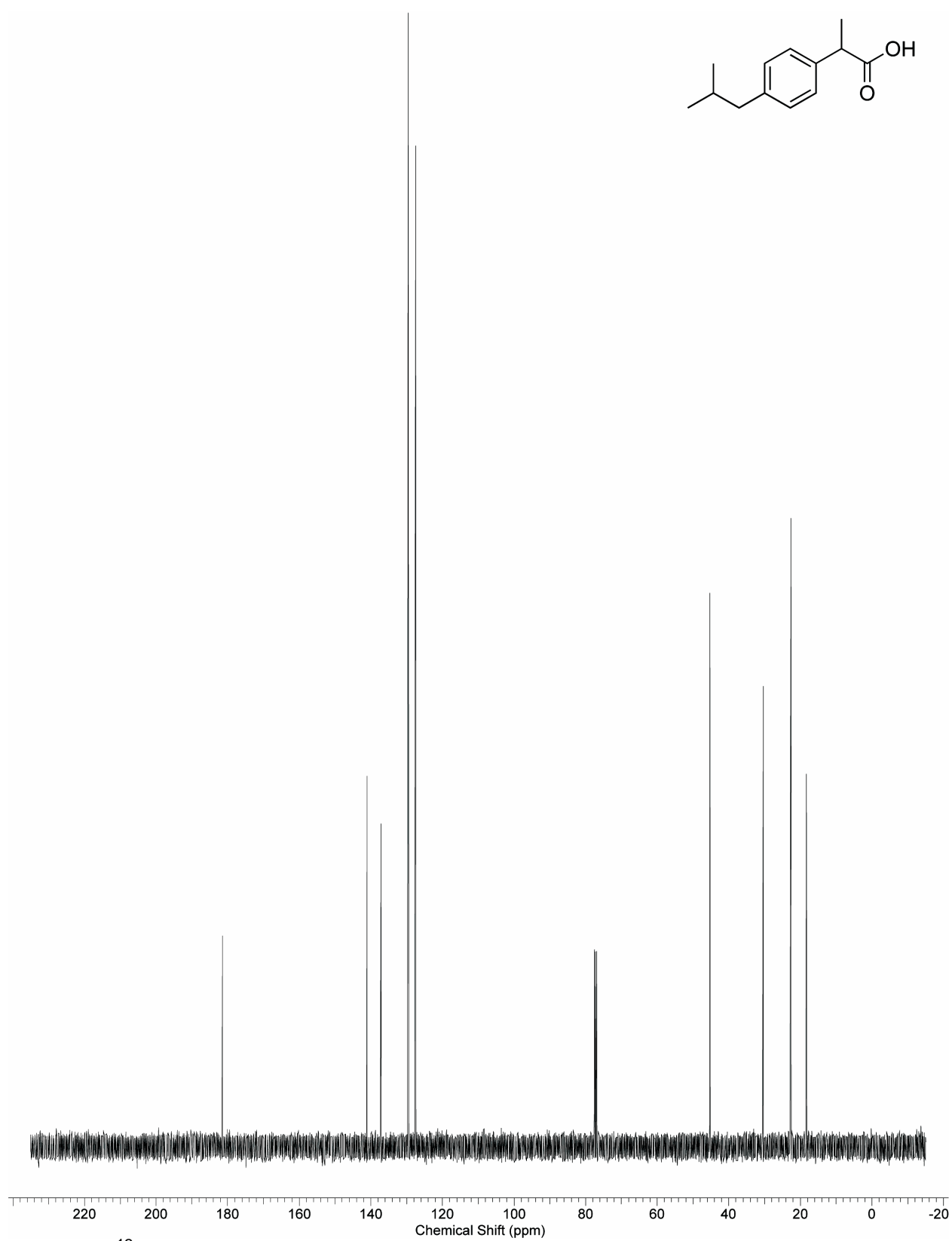
### **III. PROPOSED WORK FOR UPCOMING REPORTING PERIOD**

- § Procurement of HPLC.
- § Purity comparison of synthesized ibuprofen and authentic sample ( $^1\text{H}$  and  $^{13}\text{C}$  NMR and GC).
- § Complete batch synthesis of atropine.
- § Establish design characteristics for the prototype flow reactor.
- § Begin exploratory investigation of ibuprofen synthesis in flow using in-house prototype.
- § Atom economy and E-factor analysis of ibuprofen synthesized in batch.
- § Atom economy and E-factor analysis of atropine synthesized in batch.
- § Purity comparison of synthesized atropine and authentic sample ( $^1\text{H}$  and  $^{13}\text{C}$  NMR and GC).

## Appendix of Characterization Data

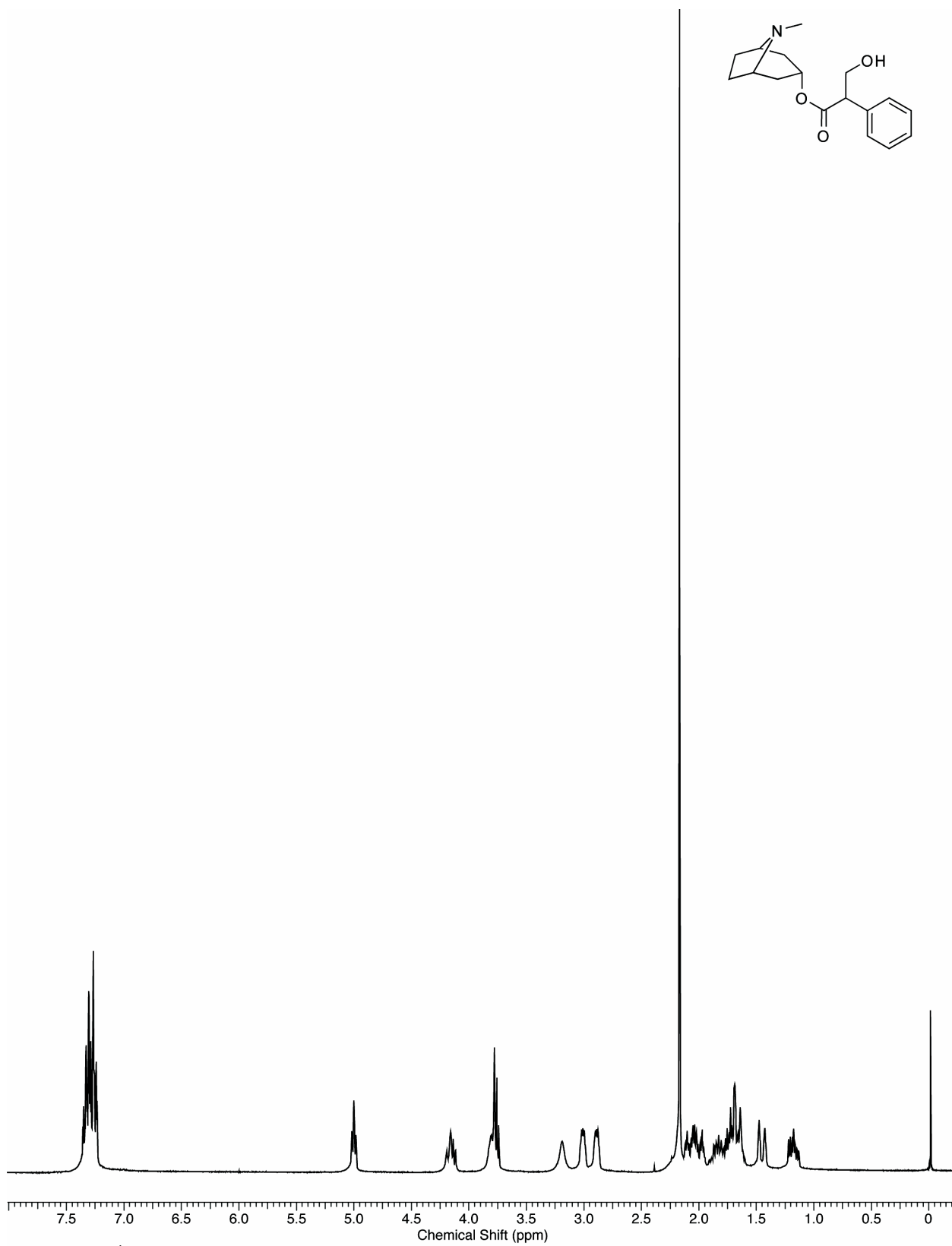


**Figure 1.**  $^1\text{H}$  NMR spectrum of an authentic sample of ibuprofen.

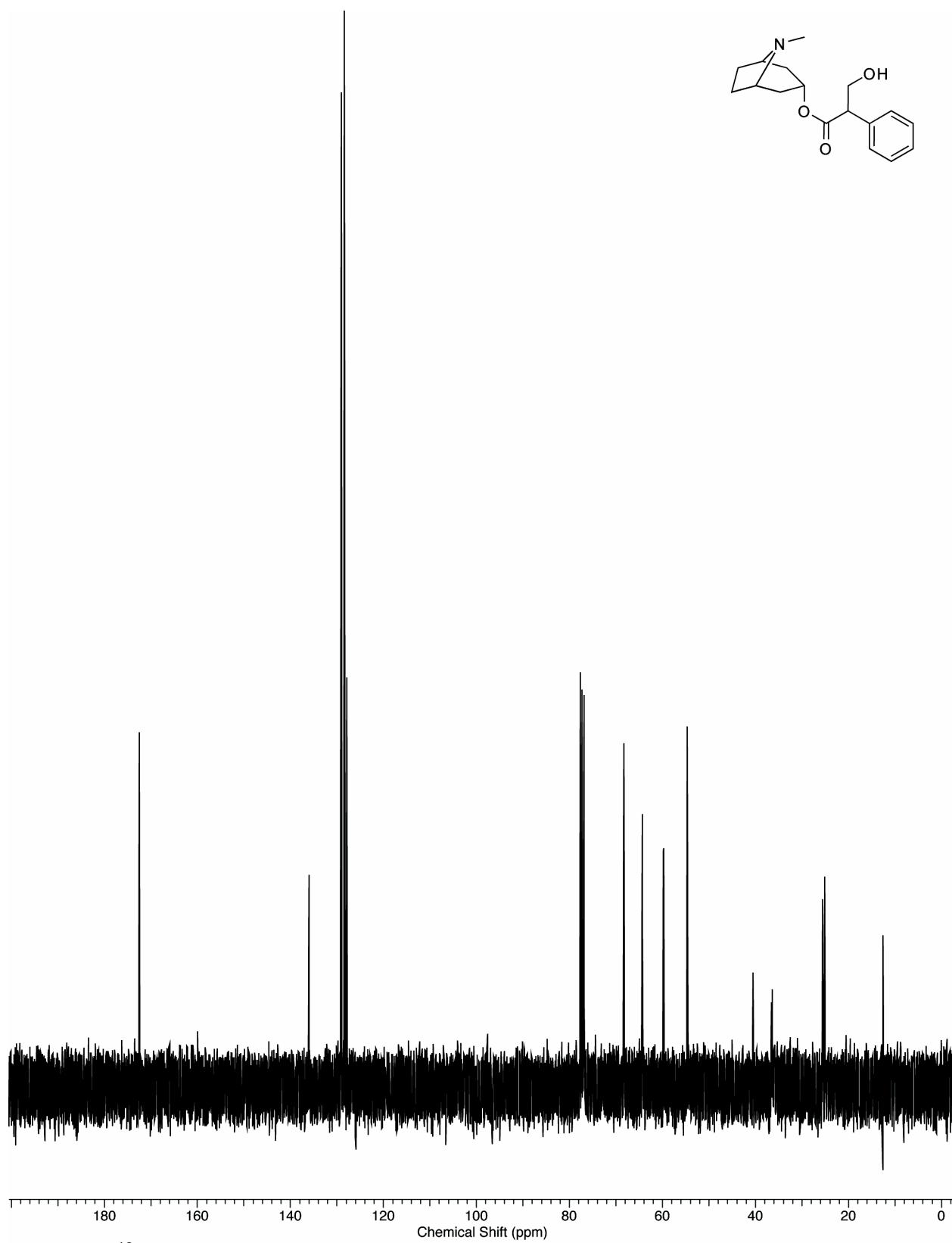


**Figure 2.**  $^{13}\text{C}$  NMR spectrum of an authentic sample of ibuprofen.





**Figure 3.**  $^1\text{H}$  NMR spectrum of an authentic sample of atropine.



**Figure 4.**  $^{13}\text{C}$  NMR spectrum of an authentic sample of atropine.

## Task List for Overall POD Project

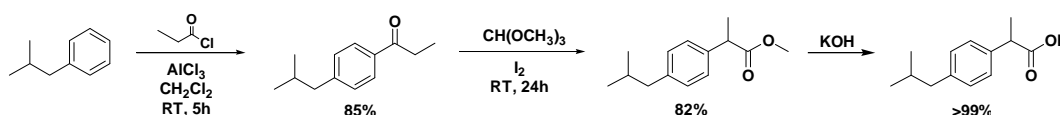
Task 1	Synthetic Route Study	Status
	Route Development on Paper (3 APIs)	ü
	Ibuprofen	ü
	Atropine	ü
	Ciprofloxacin	ü
	Atom Economy Analysis (3 APIs)	ü
	Ibuprofen	ü
	Atropine	ü
	Ciprofloxacin	ü
	Develop Analytical Foundation (2 APIs)	ü
	Ibuprofen	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	
	GC Analysis	ü
	Atropine	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	
Task 2	Initial Demonstration of Synthesis	Status
	Batch Synthesis of Ibuprofen	ü
	Complete Total Synthesis	ü
	Optimize Reaction Yield	ü
	Characterization of Final Product	ü
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	
	GC Analysis	ü
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	
	Batch Synthesis of Atropine	
	Complete Total Synthesis	
	Optimize Reaction Yield	
	Characterization of Final Product	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	
	HPLC Analysis	
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	
Task 3	Prototype Demonstration of Synthesis	Status
	Design Flow Reactor	
	Perform Chemistry in Prototype (2 APIs)	
	Ibuprofen	
	Complete Total Synthesis	
	Characterization of Final Product	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	
	HPLC Analysis	
	GC Analysis	
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	
	Atropine	
	Complete Total Synthesis	
	Characterization of Final Product	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	
	HPLC Analysis	
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	

## Appendix 2 – Systanix Second Progress Report

### I. FEASIBILITY ASSESSMENT: BATCH CHEMISTRY

#### A. Ibuprofen

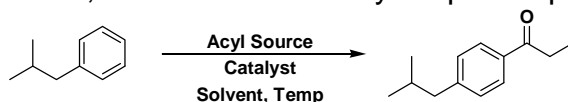
We previously reported the successful synthesis of ibuprofen in batch mode with an overall yield of 70% (Scheme 1). The first step in this process employs a stoichiometric amount of aluminum chloride and therefore generates a significant amount of waste upon reaction work-up. Replacing this method with one employing a truly catalytic (ideally <20 mol%) procedure would be a considerable advance toward the goals of the POD project by reducing the amount of material that needs to be transported into the field as well as reducing the amount of waste produced at the site of production.



**Scheme 1.** Overall synthesis of ibuprofen performed in batch mode.

#### 1. Attempted Catalytic Friedel-Crafts Routes

This section describes the unsuccessful attempts at completing the first step of the ibuprofen synthesis using various catalysts to complete the Friedel-Crafts acylation. A variety of catalysts described in the literature were either synthesized or purchased and screened in the reaction described in Scheme 2. As can be seen in Table 1, none of these catalytic species proved to be effective.



**Scheme 2.** The catalytic Friedel-Crafts acylation of isobutylbenzene.

**Table 1.** Results of the catalytic Friedel-Crafts acylation of isobutylbenzene.

Catalyst	Conditions	Result
PBFTM (1 mol%)	Propionyl chloride, $\text{CH}_3\text{NO}_2$ , 50 °C	N. R.
PBFTM (1 mol%)	Propionyl chloride, $\text{CH}_3\text{NO}_2$ , 80 °C	N. R.
PBFTM (1 mol%)	Propionic anhydride, $\text{CH}_3\text{NO}_2$ , 50 °C	N. R.
PBFTM (1 mol%)	Propionic anhydride, $\text{CH}_3\text{NO}_2$ , 80 °C	N. R.
TfOH (10 mol%)	Propionyl chloride, neat, RT	N. R.
TfOH (10 mol%)	Propionyl chloride, neat, 50 °C	N. R.
TfOH (10 mol%)	Propionyl chloride, neat, 80 °C	N. R.
TfOH (10 mol%)	Propionic anhydride, neat, RT	N. R.
TfOH (10 mol%)	Propionic anhydride, neat, 50 °C	N. R.
TfOH (10 mol%)	Propionic anhydride, neat, 80 °C	N. R.
$\text{Sc}(\text{OTf})_3$ (20 mol%)	Propionic anhydride, $\text{CH}_3\text{NO}_2$ , 50 °C	N. R.

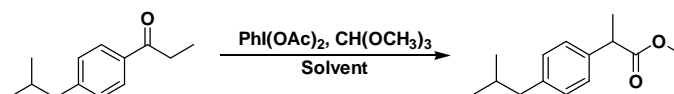
Sc(OTf)<sub>3</sub> (20 mol%)      Propionic anhydride, CH<sub>3</sub>CN, 50 °C      N. R.

PFBTM = pentafluorophenylbis(triflyl)methane

Upon further review of the literature, it was discovered that several of the proof-of-concept systems that employ these catalysts involve only highly activated aryl substrates.

## 2. (Diacetoxy)iodobenzene-mediated Rearrangement

The second step of the batch ibuprofen synthesis was markedly improved over our previous report (Scheme 3). Iodine was replaced with (diacetoxy)iodobenzene (PhI(OAc)<sub>2</sub>) as the oxidant and reaction conditions were screened. As can be seen in Table 2, the reaction was successfully performed



**Scheme 3.** PhI(OAc)<sub>2</sub>-mediated rearrangement of 4-isobutylpropiophenone.

neat, providing a quantitative yield of the resulting ester product. In addition to searching for catalytic processes, removing the need for solvent by performing reactions under neat conditions also is a major stride toward the reduction of materials that need to be transported into the field and the amount of waste that is generated on site.

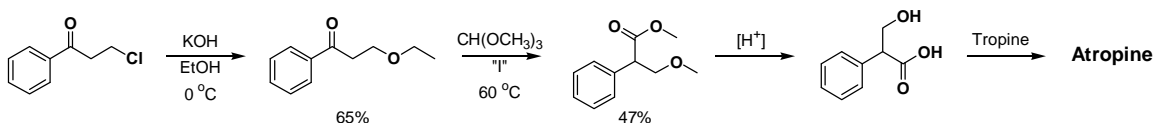
**Table 2.** Results of the PhI(OAc)<sub>2</sub>-mediated rearrangement of 4-isobutylpropiophenone.

Conditions	Conversion <sup>a</sup>
Neat, 60 °C	>99%
CH <sub>2</sub> Cl <sub>2</sub> , 40 °C	>99%
CH <sub>2</sub> Cl <sub>2</sub> , RT	>99%

<sup>a</sup> Conversion determined by GC.

## B. Atropine

Substantial progress has been made toward the batch synthesis of atropine during this work period. The first two steps have been completed, albeit with moderate yields (Scheme 4). The reaction conditions have not been optimized and therefore provide a positive outlook that this process can be made more efficient.



**Scheme 4.** Proposed Synthesis of Atropine

The first step of the process involves an ethyl ether formation. This step proved to be more problematic than expected. The elimination pathway was

often dominant, which resulted in the formation of phenyl vinyl ketone (PVK) as a byproduct. Subsequent polymerization of this material often provided an intractable reaction mixture. It was found that the reaction proceeded with the addition of an ethanolic solution of KOH at 0 °C (Table 3), as opposed to adding KOH directly to the reaction mixture. By premixing the KOH and ethanol, the exotherm was controlled and resulted in more efficient temperature control of the reaction.

**Table 3.** Results of 3-chloropropiophenone substitution.

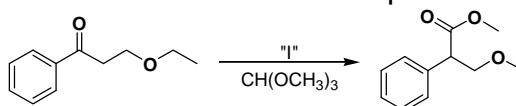
Base	Conditions	Result
KOH	EtOH, 0 °C	Minimal product formation; PVK formed as byproduct.
KOH <sup>a</sup>	EtOH, 0 °C	Minimal product formation; PVK formed as byproduct.
KOAc	EtOH, THF, reflux	NR; PVK and polymeric byproducts formed.
NaOMe	MeOH, RT	NR; PVK and polymeric byproducts formed.
KOH <sup>b</sup>	EtOH, 0 °C	65% <sup>c</sup>

<sup>a</sup> Slow addition of KOH.

<sup>b</sup> KOH and EtOH were premixed prior to addition to the reaction mixture.

<sup>c</sup> Unoptimized yield.

The iodine-mediated rearrangement step shown in Scheme 5 was also performed successfully. It was determined that the reaction could be performed using (diacetoxy)iodobenzene in neat trimethylorthoformate at 60 °C (Table 4). As with the first step, this reaction has not been optimized.



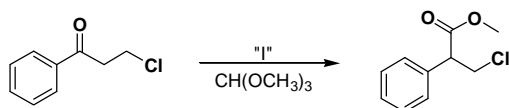
**Scheme 5.** Iodine-mediated rearrangement of 3-ethoxypropiophenone.

**Table 4.** Results of the iodine-mediated rearrangement of 3-ethoxypropiophenone.

Iodine Reagent	Conditions	Product
I <sub>2</sub>	Neat, RT	N.R.; byproduct formation
PhI(OAc) <sub>2</sub>	Neat, 60 °C	47% <sup>a</sup>

<sup>a</sup>unoptimized yield

Preliminary work on an alternative route to atropine was also carried out (Scheme 6). Success with this reaction would provide a material that could be hydrolyzed and saponified at the same time to provide tropic acid, thereby removing one step from the synthesis. At this point, this reaction has not proven to be successful (Table 5), but exploratory work is continuing on this potential shorter route to the atropine target.

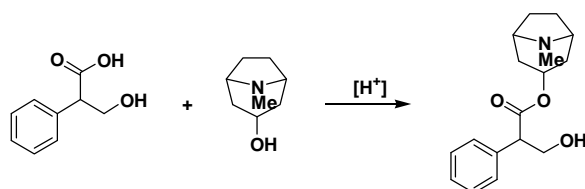


**Scheme 6.** Iodine-mediated rearrangement of 3-chloropropiophenone.

**Table 5.** Results of the iodine-mediated rearrangement of 3-chloropropiophenone.

Iodine Reagent	Conditions	Product
I <sub>2</sub>	Neat, RT	N. R.
PhI(OAc) <sub>2</sub>	Neat, 60 °C	N. R.

The following section describes unsuccessful attempts to synthesize atropine via the coupling of tropic acid and tropine (Scheme 7). A variety of acid-catalyzed methodologies were explored with no success (Table 6). It has been

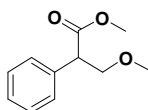


**Scheme 7.** The proposed final step of the atropine synthesis.

speculated that a byproduct formed in this reaction is the intramolecular esterification of tropic acid to provide a 4-membered lactone species. These reactions all demonstrate a significant number of other byproducts by TLC and <sup>1</sup>H-NMR spectroscopy. Future attempts to generate the ester linkage will include a transesterification with the methyl ester, methyl ether version of tropic acid that is produced as a result of the iodine-mediated rearrangement (Figure 1). Other methodologies may include protection of the tropic acid alcohol to prevent competing esterification.

**Table 6.** Results of the final step of the atropine synthesis.

Catalyst	Conditions	Result
Dowex 50W-X8-200	Neat, 120 °C	N.R.
TfOH (15 eq)	80 °C	N.R.
MeSO <sub>3</sub> H (15 eq)	Al <sub>2</sub> O <sub>3</sub> (3 eq), 80 °C	N.R.
HCl (g)	Neat, 145 °C	N.R.



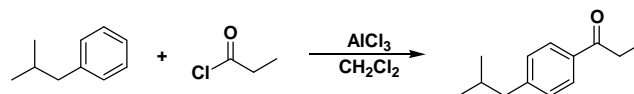
**Figure 1.** Product of the iodine-mediated rearrangement step of the atropine synthesis.

## II. FEASIBILITY ASSESSMENT: FLOW CHEMISTRY - HOMOGENEOUS

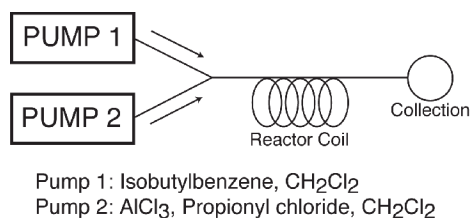
We have successfully carried out the first two steps of the ibuprofen synthesis in our microreactor using homogeneous reactions in a continuous flow manner. All reactions were run using a reactor channel with a 60 cm length and a 1.6 mm inner diameter. The information listed below describes the optimization procedure of the first two successful steps of the synthesis.

### A. Friedel-Crafts Acylation

The first step of the ibuprofen synthesis was successfully completed using a Friedel-Crafts acylation in our flow reactor (Scheme 8). A fluid stream of isobutylbenzene in dichloromethane was added to a fluid stream of aluminum chloride and propionyl chloride in dichloromethane at varying flow rates at room



**Scheme 8.** Friedel-Crafts acylation for the ibuprofen synthesis.



**Scheme 9.** Schematic of Friedel-Crafts flow acylation.

temperature (Scheme 9). A residence time of roughly 26 minutes (a total volumetric flow rate of 50  $\mu\text{L min}^{-1}$ ) was determined to be the optimal flow rate, affording quantitative conversion after optimization (Table 7). Using a 0.5 M stock solution of isobutylbenzene provides approximately 140  $\text{mg}\cdot\text{hr}^{-1}$  from a single 60 cm channel. It should be pointed out that when we identify a catalytic system for this step, the aluminum chloride reagent will be replaced for the reasons of efficiency described in Section IA.



**Table 7.** Results of Friedel-Crafts flow acylation increasing residence times.<sup>a</sup>

Eq. AlCl <sub>3</sub>	Eq. Prop. Cl	Flow Rate (mL·min <sup>-1</sup> )	Res. Time (min)	Conversion
1.5	1.0	30	42.76	76% <sup>b</sup>
1.5	1.0	40	32.07	42% <sup>b</sup>
2.0	1.0	40	32.07	82%
2.0	1.5	40	32.07	86% <sup>b</sup>
2.0	1.5	50	25.65	80%
2.0	1.5	80	16.03	83%
2.0	2.0	40	32.07	78% <sup>b</sup>
2.0	2.0	50	25.65	94% <sup>c</sup>
2.0	2.0	50	25.65	>99% <sup>d</sup>
2.0	2.0	50	25.65	>99% <sup>b,e</sup>
2.0	2.0	80	16.04	70%

<sup>a</sup> Reactions carried out using a 0.1 M stock solution of isobutylbenzene at room temperature unless otherwise noted.

<sup>b</sup> Average of two trials.

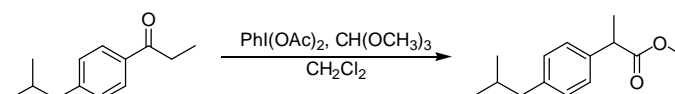
<sup>c</sup> Average of three trials.

<sup>d</sup> Using a 0.25 M stock solution of isobutylbenzene.

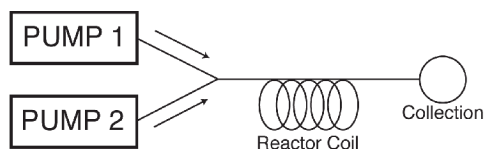
<sup>e</sup> Using a 0.5 M stock solution of isobutylbenzene.

### B. (Diacetoxy)iodobenzene-mediated Rearrangement

The second step of the ibuprofen synthesis was successfully completed using a (diacetoxy)iodobenzene-mediated oxidative rearrangement in our flow reactor (Scheme 10). A fluid stream of concentrated sulfuric acid was added to a

**Scheme 10.** (Diacetoxy)iodobenzene-mediated rearrangement.

fluid stream of 4-isobutylpropiophenone, trimethylorthoformate, and (diacetoxy)iodobenzene in dichloromethane at room temperature (Scheme 11). A residence time of roughly 10.5 minutes (a total volumetric flow rate of roughly  $122 \mu\text{L min}^{-1}$ ) was determined to be the optimal flow conditions, affording quantitative conversion to the rearranged product (Table 8).



Pump 1: 4-isobutylpropiophenone,  $\text{PhI}(\text{OAc})_2$ ,  $\text{CH}(\text{OCH}_3)_3$ ,  $\text{CH}_2\text{Cl}_2$   
Pump 2: conc.  $\text{H}_2\text{SO}_4$

**Scheme 11.** Schematic of continuous-flow homogeneous iodine-mediated rearrangement.

**Table 8.** Results of continuous-flow homogeneous iodine-mediated rearrangement for ibuprofen synthesis.<sup>a</sup>

Eq. CH(OCH <sub>3</sub> ) <sub>3</sub>	Eq. PhI(OAc) <sub>2</sub>	Eq. H <sub>2</sub> SO <sub>4</sub>	Flow Rate (mL·min <sup>-1</sup> )	Res. Time (min)	Conversion
33	1.2	2.0	141.8	9.0	91%
33	1.2	2.0	121.5	10.6	>99% <sup>b</sup>
17	1.2	2.0	121.5	10.6	94%
17	1.2	2.0	122.3	10.5	93% <sup>c</sup>

<sup>a</sup> Reactions carried out using a 0.12 M stock solution of 4-isobutylpropiophenone at room temperature unless otherwise noted.

<sup>b</sup> Average of two trials.

<sup>c</sup> Using a 0.18 M stock solution of 4-isobutylpropiophenone.

### III. FEASIBILITY ASSESSMENT: FLOW CHEMISTRY – PACKED-BED

#### A. Introduction

Systanix has another tool in our suite of technology that can be applied to this project: packed-bed microreactors. Packed-bed microreactors combine the benefits of heterogeneous catalysts (ease of removal from the reaction mixture, catalyst recycling, etc.) with the high heat transfer and mixing associated with microreactors. These attributes make applying this technology an attractive option.

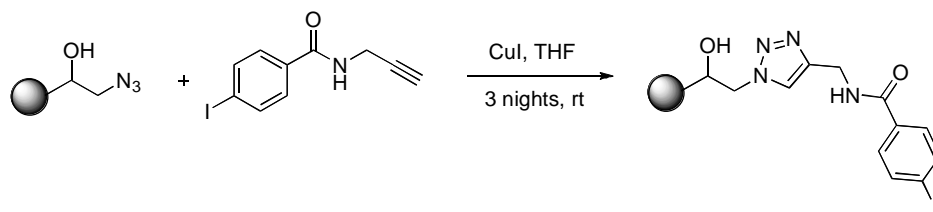
The first reaction that we investigated is the iodine-mediated oxidative rearrangement used in both the ibuprofen and atropine syntheses. As an alternative to using PhI(OAc)<sub>2</sub> for the rearrangement, we envisioned supporting the iodoso reagent to create a packed-bed reactor in which the reagent can be regenerated and recycled.

#### B. Resin Functionalization

The first step in the creation of a packed-bed microreactor is the preparation of the solid-supported reagent. We have previously demonstrated that the performance of the packed-bed microreactors is highly dependent on the solid support and it is therefore important to screen a variety of heterogeneous materials.

##### 1. Huisgen Reaction

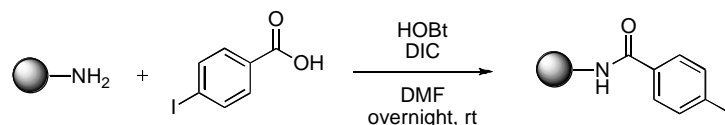
We have reported several examples of creating heterogeneous catalysts using Amberzyme Oxirane (AO) as a starting material. AO is an excellent support for continuous flow applications because it is highly solvent tolerant and does not exhibit variable swelling behavior, therefore providing predictable flow behavior. Utilizing a published methodology, a solid-supported iodobenzene derivative was prepared using “click chemistry” (Scheme 12).



**Scheme 12.** Resin functionalization via Huisgen reaction.

## 2. Amide Formation

We also decided to functionalize several amine-containing resins using standard peptide coupling procedures (Scheme 13). Three resins were functionalized: aminomethyl polystyrene, JandaJel (polystyrene core functionalized with poly(ethylene glycol) chains), and an amine version of AO.



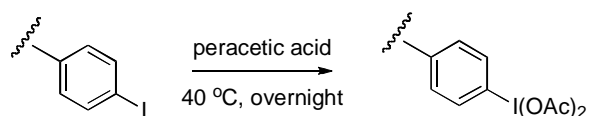
**Scheme 13.** General resin functionalization via amide formation.

## 3. Iodination of Polystyrene

Another approach involved the direct iodination of unfunctionalized polystyrene resin (2% DVB) using  $I_2$ ,  $I_2O_5$ ,  $CCl_4$ ,  $H_2SO_4$ , and nitrobenzene.

## C. Oxidation

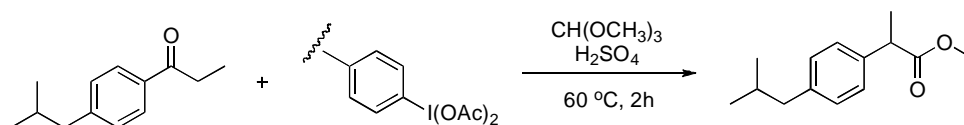
Once all the iodinated species were obtained, oxidation was performed by treating the resins with peracetic acid at 40 °C with agitation (Scheme 14). Washing and drying provides the solid-supported (diacetoxy)iodobenzene reagent.



**Scheme 14.** General oxidation of resin-supported iodoso reagents.

## D. Reaction Screening in Batch Mode

The prepared resins were analyzed for iodine content by elemental analysis and screened for activity using the reaction described in Scheme 15. These reactions were carried out in batch due to the ability to rapidly setup several small-scale reactions that do not consume significant amounts of the resins. It can be seen in Table 9 that several of the resins demonstrated activity and the AO amide was recycled successfully. These experiments are in the preliminary stage and will be expanded upon during the next work period.



**Scheme 15.** Rearrangement of 4-isobutylpropiophenone mediated by a heterogeneous iodoso reagent.

**Table 9.** Results of 4-isobutylpropiophenone rearrangement performed in batch mode using various solid-supported iodoso reagents.

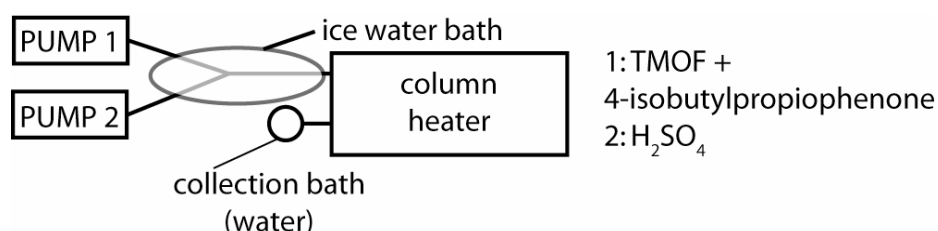
Resin	Loading (mmol/g) <sup>a</sup>	Function? <sup>b</sup>	Recyclable
Amberzyme (Huisgen)	0.14	Yes	No
Polystyrene (amide)	1.0	Yes	No
JandaJel	Not determined	No	No
Amberzyme (amide)	0.56-0.68	Yes	Yes
Polystyrene (iodinated)	0.7	Yes	?

<sup>a</sup> Determined by elemental analysis.

<sup>b</sup> Conversion is extremely variable. Almost complete conversion was achieved initially, but has dropped significantly in recent attempts. This may be due to poor oxidation conditions (AcOOH oxidation is temperature sensitive). Success using (diacetoxy)iodobenzene indicates this transformation should work if the resin is properly oxidized.

### E. Initial Reaction Attempt in Flow Mode

Initial attempts at performing this rearrangement with a packed-bed microreactor have been met with mixed success (Scheme 16). The resin chosen to support the iodoso reagent is the Amberzyme amine. It is necessary to cool the reagents to minimize gas generation due to heat formation when the fluid streams are mixed. We have been able to form product in flow, but more efficient heat control is required to achieve satisfactory conversions.



**Scheme 16.** Schematic of heterogeneous rearrangement (tubing inside column heater is packed with Amberzyme amide-supported iodoso reagent).

#### IV. STATUS OF WORK PROPOSED FOR THIS REPORTING PERIOD

- § Procurement of HPLC.  
*The order has been placed.*
- § Purity comparison of synthesized ibuprofen and authentic sample ( $^1\text{H}$  and  $^{13}\text{C}$  NMR and GC).  
*Completed.*
- § Complete batch synthesis of atropine.  
*First two steps of process have been completed (50% of process).*
- § Establish design characteristics for the prototype flow reactor.  
*General reactor dimensions and characteristics were identified during an on-site (Ithaca, NY) visit.*
- § Begin exploratory investigation of ibuprofen synthesis in flow using in-house prototype.  
*Two of the three steps of the synthesis of ibuprofen have been successfully completed in our flow reactor.*
- § Atom economy and E-factor analysis of ibuprofen synthesized in batch.  
*Not performed – awaiting optimization of the first synthetic step (FC acylation).*
- § Atom economy and E-factor analysis of atropine synthesized in batch.  
*Not performed because the synthesis was not completed.*
- § Purity comparison of synthesized atropine and authentic sample ( $^1\text{H}$  and  $^{13}\text{C}$  NMR and GC).  
*Ibuprofen was compared; atropine was not.*

#### V. PROPOSED WORK FOR UPCOMING REPORTING PERIOD

- § Finish the synthesis of ibuprofen in microreactor.
- § Compare the efficiency of the two ibuprofen syntheses: batch vs. flow.
- § Complete the synthesis of atropine in batch mode.
- § Compare purity of commercial vs. synthesized atropine.
- § Continue investigating catalytic alternative to FC acylation step.
- § Explore heterogeneous catalysts for iodine-mediate rearrangement.
- § Receive and setup HPLC.

## Task List for Overall POD Project

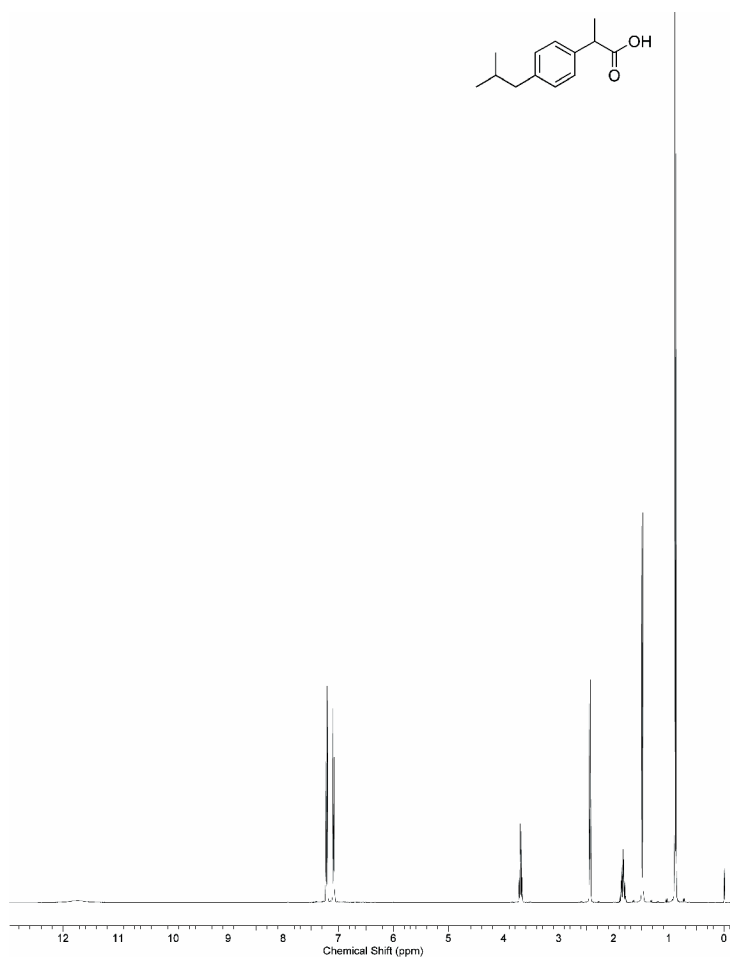
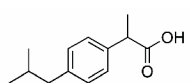
Task 1	Synthetic Route Study	Status
	Route Development on Paper (3 APIs)	ü
	Ibuprofen	ü
	Atropine	ü
	Ciprofloxacin	ü
	Atom Economy Analysis (3 APIs)	ü
	Ibuprofen	ü
	Atropine	ü
	Ciprofloxacin	ü
	Develop Analytical Foundation (2 APIs)	ü
	Ibuprofen	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	
	GC Analysis	ü
	Atropine	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	
Task 2	Initial Demonstration of Synthesis	Status
	Batch Synthesis of Ibuprofen	ü
	Complete Total Synthesis	ü
	Optimize Reaction Yield	ü
	Characterization of Final Product	ü
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	
	GC Analysis	ü
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	
	Batch Synthesis of Atropine	
	Complete Total Synthesis	1/2
	Optimize Reaction Yield	
	Characterization of Final Product	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	
	HPLC Analysis	
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	
Task 3	Prototype Demonstration of Synthesis	Status
	Design Flow Reactor	ü
	Perform Chemistry in Prototype (2 APIs)	
	Ibuprofen	2/3
	Complete Total Synthesis	
	Characterization of Final Product	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	
	HPLC Analysis	
	GC Analysis	
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	
	Atropine	
	Complete Total Synthesis	
	Characterization of Final Product	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	
	HPLC Analysis	
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	

## **COMPARISON OF NMR SPECTRA FOR SYNTHESIZED AND COMMERCIAL IBUPROFEN**

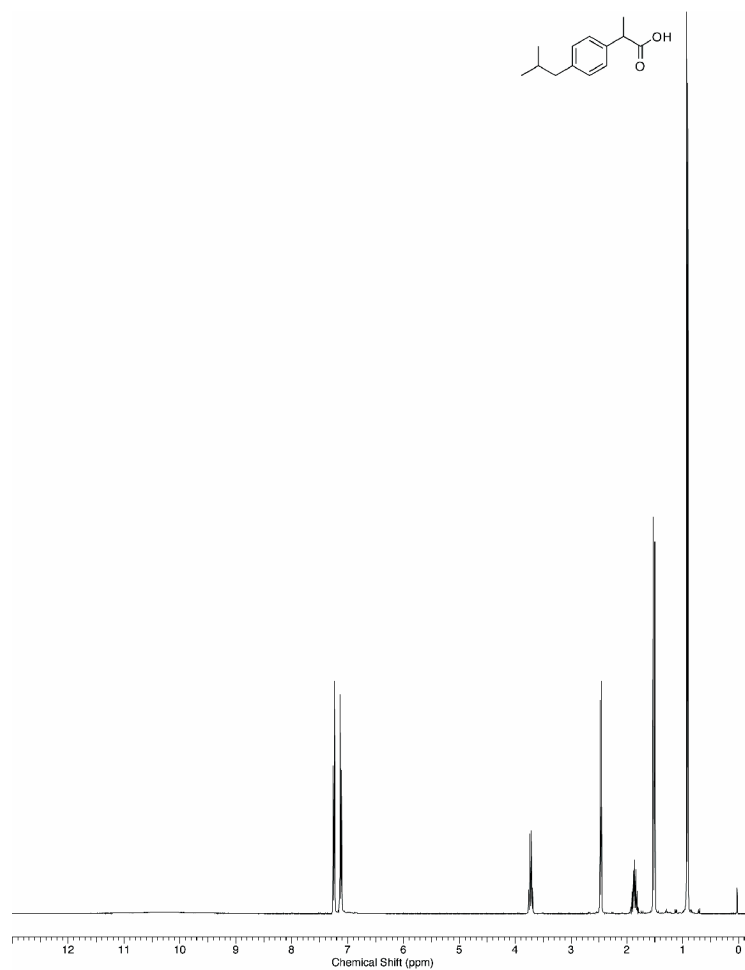
### **A. $^1\text{H}$ NMR Spectra**

1. Commercial

2. Synthesized



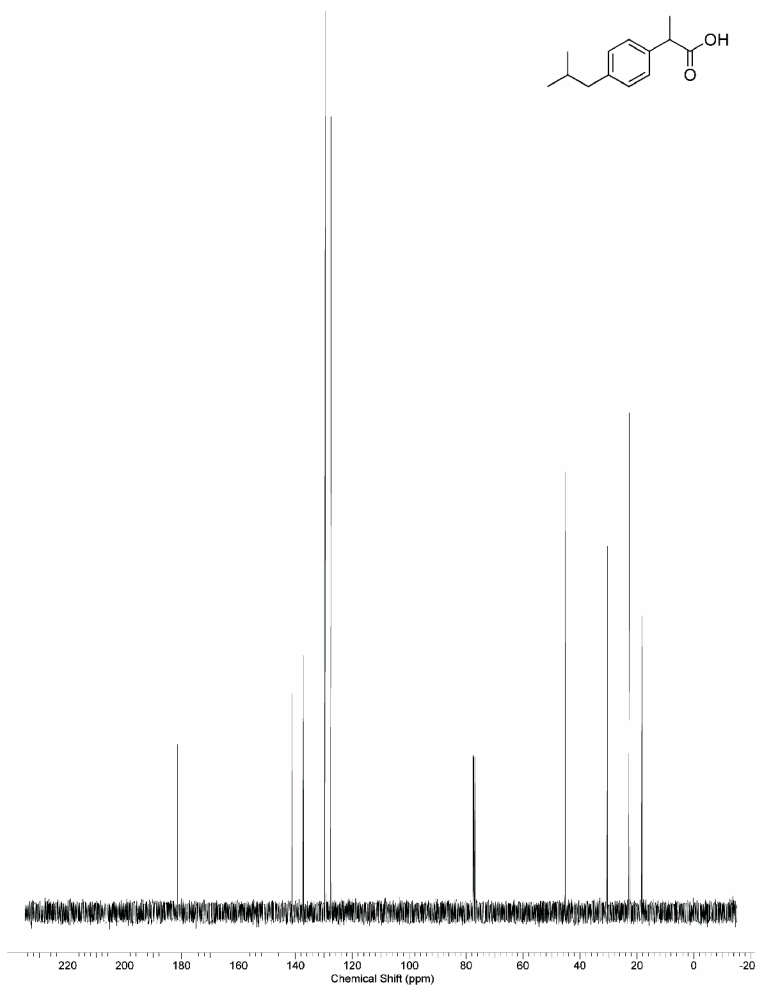
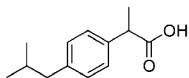


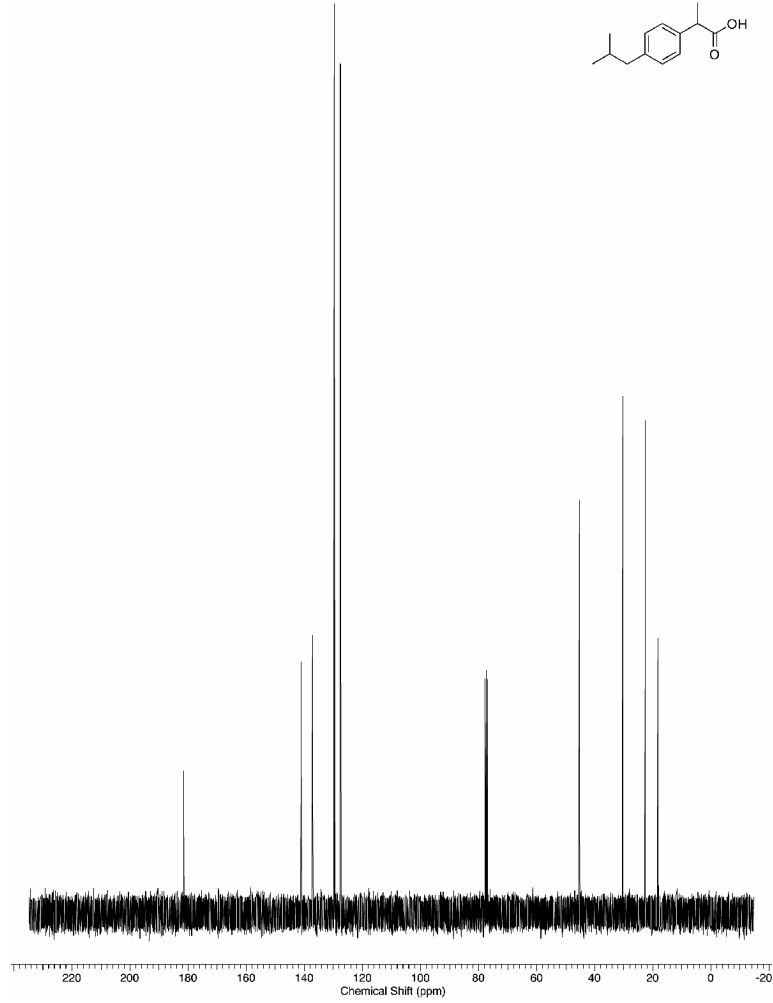
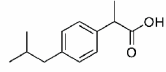


## B. $^{13}\text{C}$ NMR Spectra

1. Commercial

2. Synthesized





## Appendix 3 – Systanix Third Progress Report

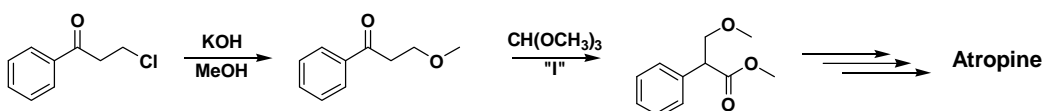
### I. FEASIBILITY ASSESSMENT: BATCH CHEMISTRY

#### A. Ibuprofen

The batch synthesis of ibuprofen was completed during the last reporting period. One attempt at greening the reaction conditions was made by replacing dichloromethane with 2-methyl THF in the Friedel-Crafts acylation. Unfortunately, the reaction did not proceed successfully in this solvent. There have been no attempts to optimize these batch conditions as the yields are respectable. Instead, efforts have been focused on the synthesis of ibuprofen in flow and the synthesis of atropine.

#### B. Atropine

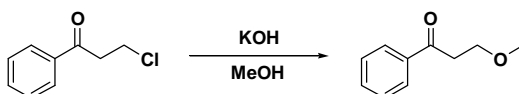
The first two steps in the synthesis of atropine (Scheme 1) that were described in the last progress report have been substantially improved, both in the context of product yield and energy consumption.



**Scheme 1.** Beginning of proposed synthesis of atropine.

#### 1. Williamson Ether Synthesis

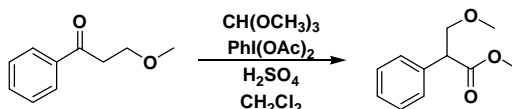
Using Buzz's suggestion of forming the methyl ether (as opposed to the ethyl ether), the reaction proceeded rapidly at 0 °C to provide the desired product in 97% yield (Scheme 2). This is a dramatic improvement over the previous yield of 65%.



**Scheme 2.** Williamson ether synthesis to form 3-methoxypropiophenone.

#### 2. (Diacetoxy)iodobenzene-mediated Rearrangement

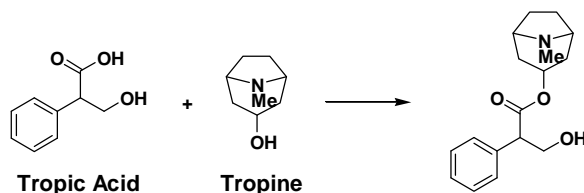
The yield of the previously reported rearrangement shown in Scheme 3 was increased to 67%, up from 47%. In addition, it was discovered that this transformation could be carried out at room temperature, as opposed to the literature-reported 60 °C. In the context of carrying out chemistry in the field, room temperature reactions are advantageous because of the reduced energy requirement.



**Scheme 3.** (Diacetoxy)iodobenzene-mediated rearrangement of 3-methoxypropiphenone.

### 3. Coupling of Tropic Acid and Tropine

A majority of the effort put forth during this reporting period was focused on the final step of the atropine synthesis – the coupling of tropic acid and tropine (Scheme 4). Several attempts were made to identify appropriate reaction conditions but none resulted in any appreciable success (Table 1). It would be beneficial to use acid catalysis for this step to obviate the need for wasteful coupling reagents, but it may be necessary to activate the carboxylic acid in situ. This portion of the atropine synthesis has proven to be more difficult than expected and **it would be helpful to get Buzz's perspective on this chemistry.**



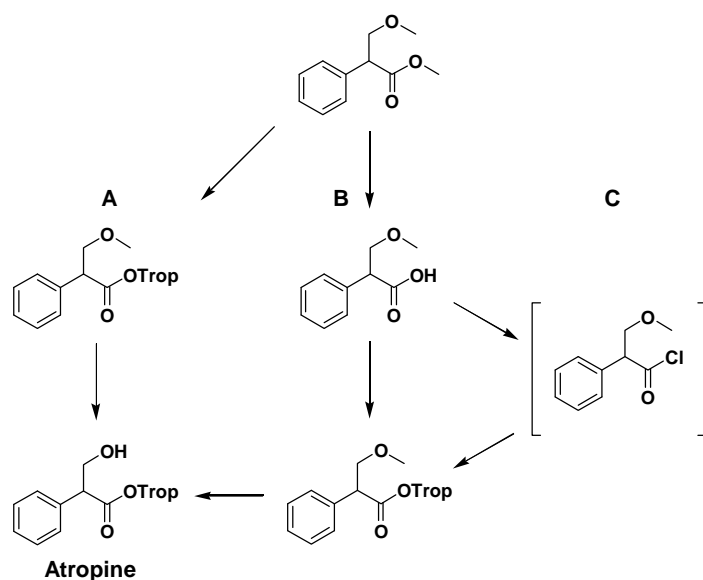
**Scheme 4.** Coupling of tropic acid and tropine to form atropine.

**Table 1.** Results of the coupling of tropic acid and tropine.

Catalyst	Reaction Conditions	Result
H <sub>2</sub> SO <sub>4</sub>	80 °C	N.R.
-	Dean-Stark	N.R.
H <sub>2</sub> SO <sub>4</sub>	Dean-Stark	N.R.
H <sub>2</sub> SO <sub>4</sub>	3 Å mol. sieves, 90 °C	N.R.
Me <sub>3</sub> SiCl	RT	N.R.
-	DCC, DMAP	N.R.

### 4. Alternative Routes to Atropine

We are currently exploring three possible solutions to the problems that have been encountered with finishing the atropine synthesis. The first route involves a transesterification of the methyl ester product of the iodine-mediated rearrangement (Scheme 5A). Subsequent cleavage of the methyl ether would liberate the unprotected alcohol and result in the formation of atropine. We have identified literature precedence for the selective demethylation of a methyl ether in the presence of ester functionalities using boron tribromide at low temperature. The second route involves saponification of the methyl ester, followed by esterification with tropine (Scheme 5B). Finally, the route described in Scheme 5C involves saponification, followed by activation of the resulting carboxylic acid to facilitate ester formation with tropine. **Input from Buzz on these possible routes would be helpful.**



**Scheme 5.** Alternative routes to synthesize atropine currently being explored: A) transesterification; B) esterification; C) esterification using an activated carboxylic acid.

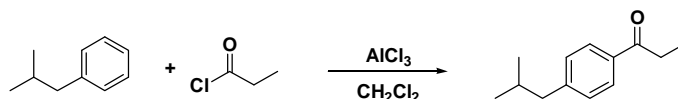
## II. FEASIBILITY ASSESSMENT: FLOW CHEMISTRY

### A. Ibuprofen

At the time of the last report, the first two steps of the ibuprofen synthesis had been successfully carried out in our microreactor. During this work period, we have successfully completed the synthesis of ibuprofen in our microreactor with an overall yield of 85%. In addition, the yields and efficiencies of the first two steps have been improved.

#### 1. Friedel-Crafts Acylation

The first step of the synthesis is the Friedel-Crafts acylation shown in Scheme 6. It was possible to reduce the number of equivalents of aluminum trichloride and propionyl chloride by 25% (from 2.0 eq. to 1.5 eq.) (Table 2). We have also optimized this reaction to operate at a faster flow rate (a 20% increase).



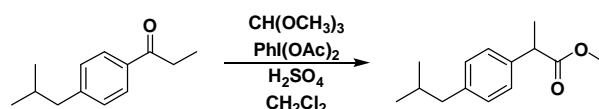
**Scheme 6.** Friedel-Crafts acylation of isobutylbenzene.

**Table 2.** Optimization of Friedel-Crafts acylation.

Flow Rate ( $\mu\text{L}/\text{min}$ )	Eq. $\text{AlCl}_3$	Eq. Prop. Cl.	Conversion
50	1.5	1.5	98%
40	1.5	1.5	97%
60	1.5	1.5	<b>98%</b>
65	1.5	1.5	97%

## 2. (Diacetoxy)iodobenzene-mediated Rearrangement

Significant optimization was achieved for the second step of the ibuprofen synthesis (Scheme 7). The number of equivalents of trimethyl orthoformate was reduced from 17 equivalents to 2 equivalents (almost an order of magnitude reduction) while maintaining a high yield of 96%, albeit at a lower flow rate (Table 3). This is a prime example of the flexibility of the microreactor approach. If efficiency is the most important metric, fewer equivalents of reagents can be used and the flow rate of the microreactor can be decreased to achieve high yields. However, if there is a situation where output is more important than efficiency, then the flow rates can be increased if more equivalents of reagents are used. This ability to tailor the chemistry to meet the desired goals will prove extremely useful in the field.



**Scheme 7.** (Diacetoxy)iodobenzene-mediated rearrangement.

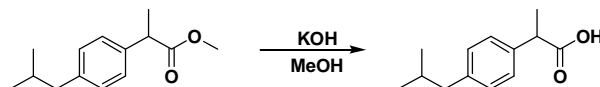
**Table 3.** Results of the (diacetoxy)iodobenzene-mediated rearrangement.

Stock <sup>a</sup> Flow Rate (μL/min)	H <sub>2</sub> SO <sub>4</sub> Flow Rate (μL/min)	Eq. PhI(OAc) <sub>2</sub>	Eq. CH(OCH <sub>3</sub> ) <sub>3</sub>	Eq H <sub>2</sub> SO <sub>4</sub>	Conv.
110	2.07	1.2	13.50	2.0	>99%
110	2.07	1.2	9.80	2.0	97%
60	1.13	1.2	5.10	2.0	>99%
45	0.85	1.2	3.00	2.0	93%
35	0.66	1.2	3.05	2.0	87%
55	1.04	1.2	3.05	2.0	>99%
55	1.04	1.2	2.05	2.0	94%
45	0.85	1.2	2.05	2.0	<b>96%</b>

<sup>a</sup>Stock includes 4-isobutylpropiophenone, PhI(OAc)<sub>2</sub> and CH(OCH<sub>3</sub>)<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>

## 3. Saponification

During this work period the final step in the ibuprofen synthesis has been successfully carried out using our microreactor (Scheme 8). Using a methanolic solution of potassium hydroxide, the resulting carboxylic acid was obtained in an unoptimized yield of 88% (Table 4).



**Scheme 8.** Saponification to produce ibuprofen.

**Table 4.** Results of the final step of the ibuprofen synthesis.

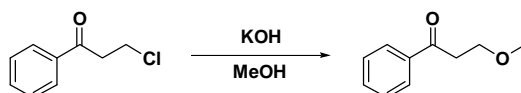
Total Flow Rate ( $\mu\text{L}/\text{min}$ )	Eq. KOH	Isolated Yield
50	5	88%

## B. Atropine

Substantial progress has been made toward the continuous flow synthesis of atropine. The microreactor-based synthesis has encountered the same problems that exist with the batch synthesis, with the tropine esterification remaining a challenge.

### 1. Williamson Ether Synthesis

The Williamson ether synthesis was carried out using our microreactor to provide the desired product in 98% yield (Scheme 9). In addition, this transformation was carried out at room temperature. This obviates the need to cool the reaction, which is necessary in batch mode. As can be seen in Table 5, the reaction output was optimized by screening a range of flow rates and the conditions that provided the highest output and the highest yield is bolded.

**Scheme 9.** Williamson ether synthesis to form 3-methoxypropyl phenyl ether.**Table 5.** Results of the Williamson ether synthesis to form 3-methoxypropyl phenyl ether.

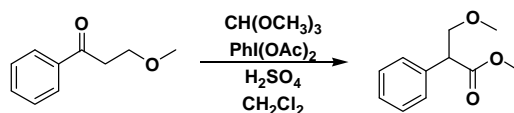
Total Flow Rate ( $\mu\text{L}/\text{min}$ ) <sup>a</sup>	Eq KOH	Conversion
100	1.5	>99%
120	1.5	98%
130	1.5	<b>98%</b>
150	1.5	94%

<sup>a</sup>0.2M starting material, 0.3M KOH

### 2. (Diacetoxy)iodobenzene-mediated Rearrangement

The rearrangement of 3-methoxypropyl phenyl ether was successfully performed using our microreactor (Scheme 10). Although a high yield of 97% was achieved, this reaction has not been optimized to determine what the minimal equivalents of reagents are necessary (Table 6). Given the success with the iodine-mediated rearrangement in the ibuprofen synthesis, we feel that this step also has the potential for drastic improvement.





**Scheme 10.** (Diacetoxy)iodobenzene-mediated rearrangement of 3-methoxypropiphenone.

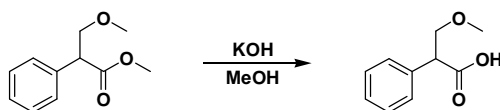
**Table 6.** Results of the (diacetoxy)iodobenzene-mediated rearrangement of 3-methoxypropiphenone.

Stock <sup>a</sup> Flow Rate (μL/min)	H <sub>2</sub> SO <sub>4</sub> Flow Rate (μL/min)	Eq. PhI(OAc) <sub>2</sub>	Eq. CH(OCH <sub>3</sub> ) <sub>3</sub>	Eq H <sub>2</sub> SO <sub>4</sub>	Yield
130	2.45	1.2	13.5	2.0	97%

<sup>a</sup>Stock includes 3-methoxypropiphenone, PhI(OAc)<sub>2</sub> and CH(OCH<sub>3</sub>)<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>

### 3. Ester Saponification

As described in Schemes 5B and 5C, one possible route to atropine involves the coupling of tropine and the methylated version of tropic acid. These routes begin with hydrolyzing the methyl ester shown in Scheme 11. This transformation was carried out smoothly in our microreactor and we obtained an unoptimized yield of 74% (Table 7).



**Scheme 11.** Saponification of methyl ester intermediate.

**Table 7.** Results of the saponification of methyl ester intermediate.

Flow Rate (μL/min)	Eq. KOH	Yield
25	5	74%

## III. EVALUATION OF REACTION EFFICIENCY

In order to evaluate the most efficient methods of producing ibuprofen and atropine, it is essential to compare reaction metrics for each respective route. This process has begun and will be completed once all syntheses are completed and optimized. Once this point is reached, each reaction will be performed on a larger scale in order to obtain values for materials used in the reaction, as well as the work-up. This will alleviate problems associated with evaluating reaction efficiency on the small scale, including using excess solvent and chromatographic material during the purification step. **Input from Buzz will enable this process to be performed more effectively.**

#### IV. STATUS OF EQUIPMENT

The order for the GC and the HPLC has been placed to Varian and the ship date is scheduled for August 14<sup>th</sup>. Once this equipment is in place, the HPLC evaluation of product purity will be carried out.

#### V. STATUS OF WORK PROPOSED FOR THIS REPORTING PERIOD

- § Finish the synthesis of ibuprofen in microreactor.  
*Completed.*
- § Compare the efficiency of the two ibuprofen syntheses: batch vs. flow.  
*In progress.*
- § Complete the synthesis of atropine in batch mode.  
*Approximately half complete.*
- § Compare purity of commercial vs. synthesized atropine.  
*Not possible until synthesis is completed.*
- § Continue investigating catalytic alternative to FC acylation step.  
*No catalysts were found to be effective.*
- § Explore heterogeneous catalysts for iodine-mediate rearrangement.  
*Inconsistency with the solid-supported reagents caused us to put this goal on the back burner.*
- § Receive and setup HPLC.  
*The order has been placed and the shipment date is Aug. 14.*

#### VI. PROPOSED WORK FOR UPCOMING REPORTING PERIOD

- § Compare the efficiency of the two ibuprofen syntheses: batch vs. flow.
- § Complete the synthesis of atropine in batch mode.
- § Complete the synthesis of atropine in flow.
- § Compare the efficiency of the two atropine syntheses: batch vs. flow.
- § Receive and setup HPLC.
- § Compare purities of synthesized materials to commercial sources.

## Appendix 4 – Systanix Fourth Progress Report

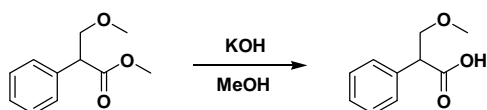
### I. FEASIBILITY ASSESSMENT: BATCH CHEMISTRY

#### A. Ibuprofen

No further advances or improvements on the previously reported batch synthesis of ibuprofen have been achieved.

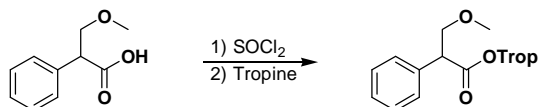
#### B. Atropine

A majority of work performed during this reporting period was focused on the synthesis of atropine in batch mode. Beginning with the product of the iodine-mediated rearrangement, the methyl ester was saponified using methanolic potassium hydroxide to provide the desired product in 88% yield (Scheme 1).



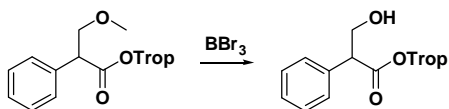
**Scheme 1.** Saponification of the iodine-mediated rearrangement product.

The resulting carboxylic acid was activated using thionyl chloride to produce an acid chloride. After removing excess thionyl chloride by distillation, the acid chloride was coupled with tropine to form the desired tropic acid ester in 52% isolated yield (Scheme 2). This methodology proved to be the first successful method of forming the important tropic acid ester linkage.



**Scheme 2.** Thionyl chloride mediated tropic acid ester formation.

The final step of the atropine synthesis relies on a boron tribromide mediated demethylation (Scheme 3). Analysis of this reaction using thin layer chromatography indicated that atropine was being formed under these conditions, however no isolated yield was obtained. It is possible that the tertiary amine in the tropine moiety was slowly being methylated by the methylbromide byproduct that is formed during the course of the reaction. This method is very promising and could be optimized (reaction time and temperature) if more time was available.



**Scheme 3.** Demethylation of atropine methyl ether to produce atropine.

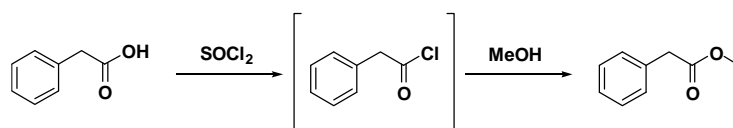
## II. FEASIBILITY ASSESSMENT: FLOW CHEMISTRY

### A. Ibuprofen

No further advances or improvements on the previously reported flow synthesis of ibuprofen have been achieved.

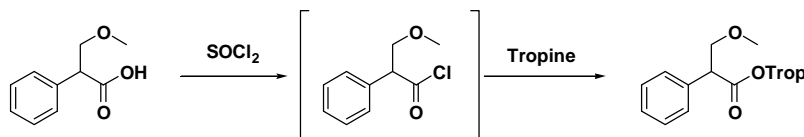
### B. Atropine

In order to develop appropriate flow reaction conditions for performing the thionyl chloride mediated ester synthesis shown in Scheme 2, we opted to use phenylacetic acid and methanol as test substrates to avoid sacrificing valuable starting material (Scheme 4). Using only one equivalent of thionyl chloride, the acid chloride was generated and subsequently quenched into methanol to provide the desired methyl ester in 96% yield. A residence time of approximately 37 minutes was required to achieve this conversion.



**Scheme 4.** Test substrates used for developing esterification flow conditions.

Applying the conditions developed above, the carboxylic acid shown in Scheme 5 was activated with thionyl chloride and quenched into a toluene solution of tropine at 80 °C. Following isolation, the desired product was obtained in a 30% yield. It is possible that the conditions for the reaction shown in Scheme 4 do not directly translate to these substrates. In any case, this reaction was performed successfully and further optimization of the reaction conditions would undoubtedly result in an increase in yield. It is also worth pointing out that the continuous flow conditions do not require excess thionyl chloride, and therefore removes the need for an intermediate distillation step.



**Scheme 5.** Two-step flow synthesis of atropine methyl ether.

### III. REACTION METRICS

The reaction metrics for ibuprofen (in batch and flow) and atropine (in flow) have been determined as much as possible with the current state of each synthesis. It is necessary to give three brief definitions of the abbreviations that are used in this discussion:

- Atom Economy (AE): Describes how much of the reactants remain in the final product. This does not account for stoichiometry or solvent; *higher atom economy values represent more efficient processes.*
- E-Factor: This describes the mass of waste generated per mass of product obtained (taken from Sheldon references); *lower E-factor values represent more efficient processes.*
- Reaction Mass Efficiency (RME): This is the percentage of the mass of reactants that remain in the final product and does account for solvent and stoichiometry. This was taken from GlaxoSmithKline; *higher RME values represent more efficient processes.*

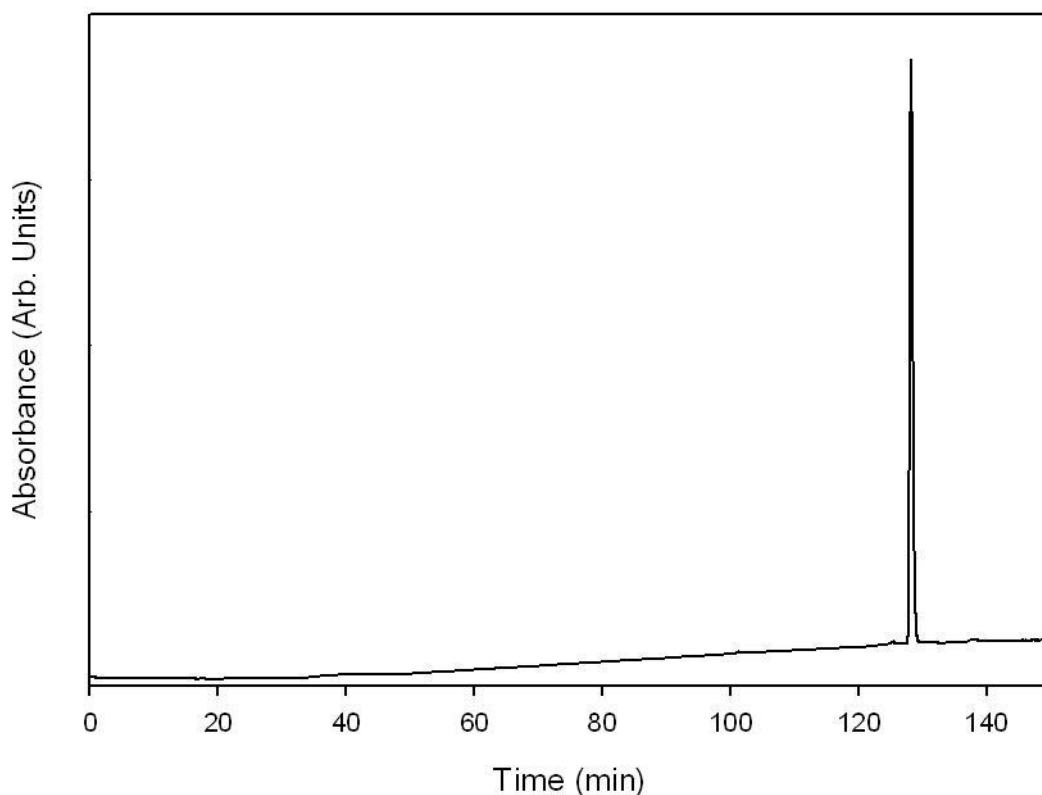
For the purposes of this discussion, work-up conditions were not included and therefore the actual E-factors will be larger and the actual RME values will be lower. An interesting point to make about the values listed in Table 1 is that the E-factor for the overall ibuprofen synthesis is roughly 3-fold less for the flow synthesis in comparison to batch, which indicates the increase in chemical efficiency achieved by using microreactors.

**Table 1.** Reaction metrics for the syntheses of ibuprofen and atropine.

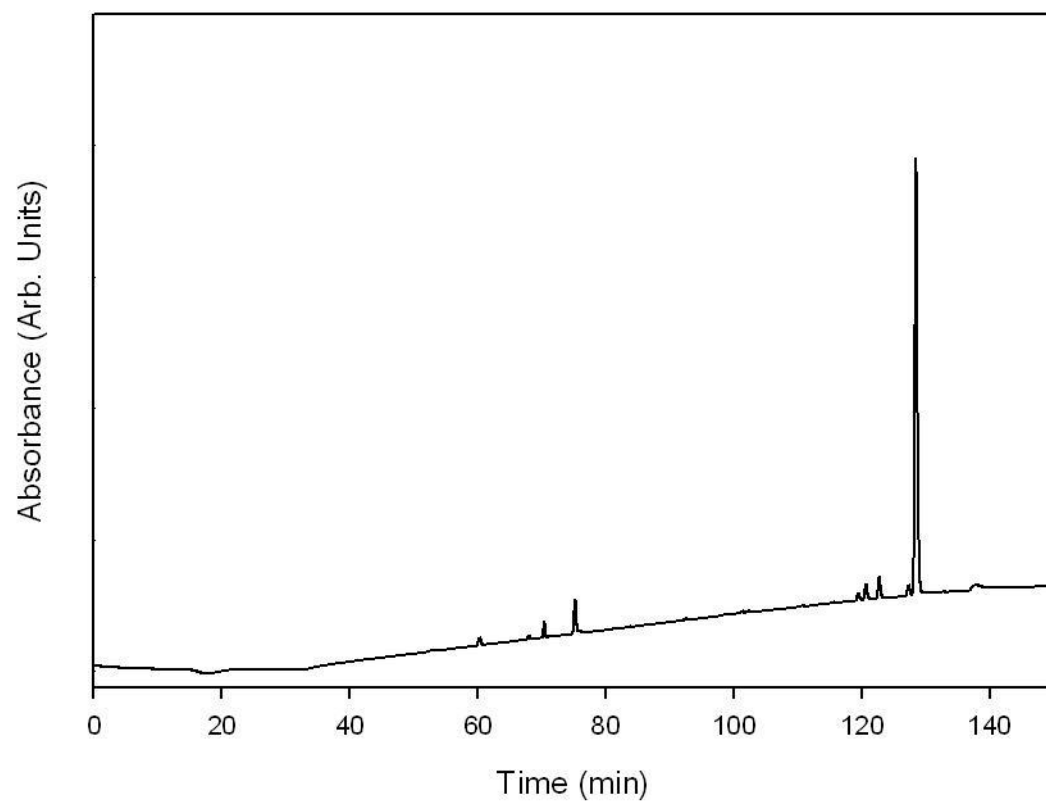
	<b>Atom Economy</b>	<b>E-Factor</b>	<b>RME</b>
Ibuprofen (batch)	0.19	25.4	0.04
Ibuprofen (flow)	0.19	8.3	0.11
Atropine (batch)	0.20	Not Calculated	Not calculated
Atropine (flow)	0.20	15.9 (1 <sup>st</sup> 3 steps)	0.06 (1 <sup>st</sup> 3 steps)

#### IV. HPLC Analysis

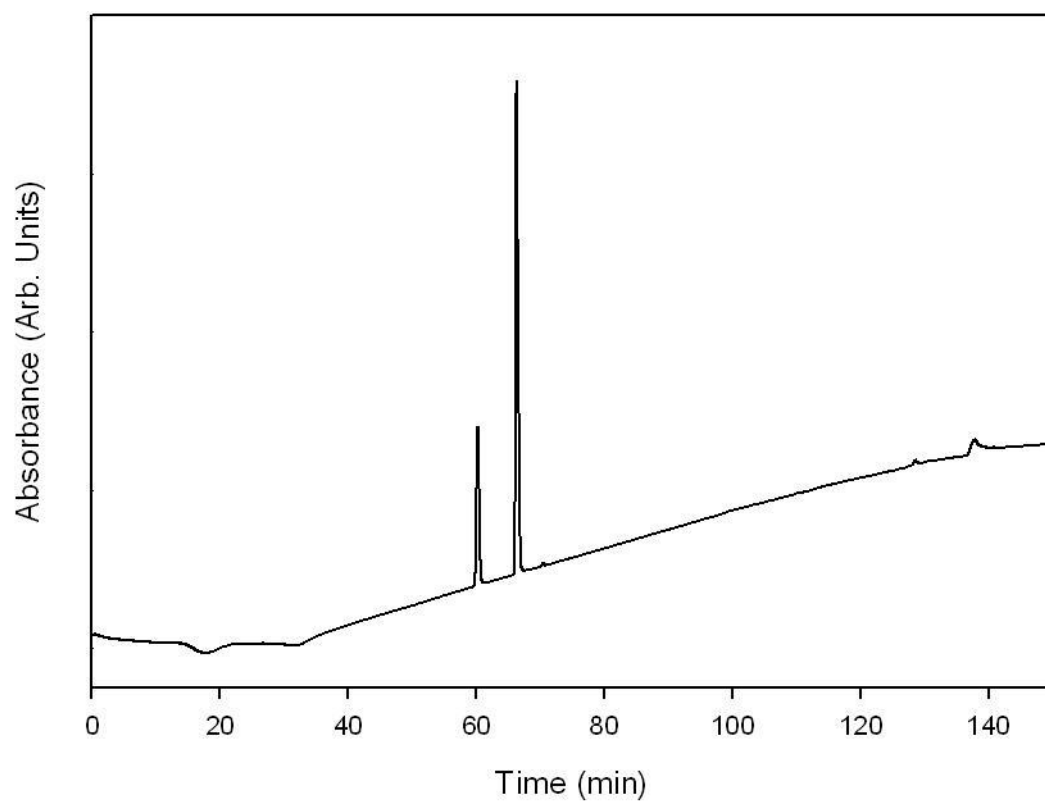
HPLC analysis was carried out to compare the purity profiles of commercially available and synthesized samples of ibuprofen, shown in Figures 1 and 2, respectively. It was determined that the synthesized sample of ibuprofen contained roughly 20% impurities as determined by relative peak areas. Since the detector used in this analysis is based on absorbance, it is necessary to have the extinction coefficients of each impurity in order to make an overall assessment of the levels of impurities. In any case, the synthesized sample had been prepared several weeks ago and it is possible that decomposition may have occurred between the time of synthesis and the time of analysis. In addition, this material was not recrystallized prior to analysis. It is expected that a freshly prepared and recrystallized sample would demonstrate an increased level of purity and would match that of an authentic sample of ibuprofen.



**Figure 1.** Results of HPLC analysis of a purchased sample of ibuprofen.



**Figure 2.** Results of HPLC analysis of a synthesized sample of ibuprofen.



**Figure 3.** Results of HPLC analysis of a purchased sample of atropine.



## Task List for Overall POD Project

Task 1	Synthetic Route Study	Status
	Route Development on Paper (3 APIs)	ü
	Ibuprofen	ü
	Atropine	ü
	Ciprofloxacin	ü
	Atom Economy Analysis (3 APIs)	ü
	Ibuprofen	ü
	Atropine	ü
	Ciprofloxacin	ü
	Develop Analytical Foundation (2 APIs)	ü
	Ibuprofen	ü
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	ü
	GC Analysis	ü
	Atropine	ü
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	ü
Task 2	Initial Demonstration of Synthesis	Status
	Batch Synthesis of Ibuprofen	ü
	Complete Total Synthesis	ü
	Optimize Reaction Yield	ü
	Characterization of Final Product	ü
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	ü
	GC Analysis	ü
	Purity Comparison to Authentic Sample	ü
	Atom Economy Analysis	ü
	Batch Synthesis of Atropine	
	Complete Total Synthesis	<sup>4</sup> / <sub>5</sub>
	Optimize Reaction Yield	
	Characterization of Final Product	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	
	HPLC Analysis	
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	
Task 3	Prototype Demonstration of Synthesis	Status
	Design Flow Reactor	ü
	Perform Chemistry in Prototype (2 APIs)	
	Ibuprofen	ü
	Complete Total Synthesis	ü
	Characterization of Final Product	ü
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	ü
	HPLC Analysis	ü
	GC Analysis	ü
	Purity Comparison to Authentic Sample	ü
	Atom Economy Analysis	ü
	Atropine	
	Complete Total Synthesis	<sup>4</sup> / <sub>5</sub>
	Characterization of Final Product	
	<sup>1</sup> H and <sup>13</sup> C NMR Analysis	
	HPLC Analysis	
	Purity Comparison to Authentic Sample	
	Atom Economy Analysis	